Pages 11669–11685

PART II

FEDERAL REGISTER

VOLUME 29 NUMBER 159

Washington, Friday, August 14, 1964

Department of Health, Education, and Welfare

Food and Drug Administration

DRUGS

Miscellaneous Amendments

Title 21—FOOD AND DRUGS

Chapter I—Food and Drug Administration, Department of Health, Education, and Welfare

SUBCHAPTER C—DRUGS

PART 148i—NEOMYCIN SULFATE

Tests and Methods of Assay and Certification

The Commissioner of Food and Drugs has evaluated the views and comments received in response to the notices of proposed rulemaking published in the FEDERAL REGISTER of May 2, 1963 (28 F.R. 4395), and has concluded that the following regulations should be issued for the certification of neomycin and neomycin-containing drugs subject to the Drug Amendments of 1962 (76 Stat. 785–787; Public Law 87–781). Therefore, pursuant to the provisions of the Federal Food, Drug, and Cosmetic Act (sec. 507, 59 Stat. 463, as amended; 21 U.S.C. 357), and under the authority delegated to him by the Secretary of Health, Education, and Welfare (21 CFR 2.90; 29 F.R. 471), Part 148i of Title 21 is revised as follows:

Sec.

148i.1 Neomycin sulfate.
148i.2 Neomycin undecylenate.
148i.3 Neomycin sulfate ointment; neomycin sulfate-_____ ointment (the blank being filled in with the established name(s) of the other active ingredient(s) present in accordance with paragraph (a)(1) of this section).
148i.4 Neomycin sulfate-betamethasone cream; neomycin sulfate-sodium dexamethasone phosphate cream; neomycin sulfate-dichlorisone acetate cream; neomycin sulfate-fluocinolone acetonide cream; neomycin sulfate-methylprednisolone acetate cream; neomycin sulfate-triamcinolone acetonide cream.
148i.5 Neomycin sulfate tablets.
148i.6 Neomycin sulfate-kaolin-pectin oral suspension; neomycin sulfate-kaolin-pectin-_____ oral suspension (the blank being filled in with the established name(s) of the other active ingredient(s) present in accordance with paragraph (a)(1) of this section).
148i.7 Neomycin sulfate-_____ nasal suspension; neomycin sulfate-_____ nasal solution (the blanks being filled in with the established name(s) of the other active ingredient(s) present in accordance with paragraph (a)(1) of this section).
148i.8 Neomycin sulfate-sodium propionate otic solution; neomycin sulfate-sodium propionate-prednisolone acetate otic solution.
148i.9 Neomycin sulfate-_____ ophthalmic suspension; neomycin sulfate-_____ ophthalmic solution (the blanks being filled in with the established name(s) of the other active ingredient(s) present in accordance with paragraph (a)(1) of this section).
148i.10 Neomycin sulfate-_____ lotion (the blank being filled in with the established name(s) of the other active ingredient(s) present in accordance with paragraph (a)(1) of this section).
148i.11 Neomycin sulfate-thihexinol methylbromide-polycarbophil tablets.
148i.12 Neomycin sulfate-hydrocortisone acetate suppositories.
148i.13 [Reserved]
148i.14 Neomycin sulfate-triamcinolone acetonide topical aerosol; neomycin sulfate-dexamethasone topical aerosol.
148i.15 Neomycin sulfate-polymyxin B sulfate-_____ ophthalmic suspension; neomycin sulfate-polymyxin B sulfate-_____ ophthalmic solution (the blanks being filled in with the established name(s) of the other active ingredient(s) present in accordance with paragraph (a)(1) of this section).
148i.16 Neomycin sulfate-polymyxin B sulfate ointment.
148i.17 [Reserved]
148i.18 Neomycin sulfate-polymyxin B sulfate-hydrocortisone otic suspension; neomycin sulfate-polymyxin B sulfate-hydrocortisone-sodium heparin otic suspension.
148i.19 Neomycin sulfate-polymyxin B sulfate-acetarsone vaginal suppositories.
148i.20 Neomycin sulfate-polymyxin B sulfate-gramicidin ophthalmic solution.
148i.21 Neomycin sulfate-polymyxin B sulfate - gramicidin - hydrocortisone-hydroxyamphetamine hydrobromide-phenylephrine hydrochloride nasal solution.
148i.22 Neomycin sulfate for prescription compounding.
148i.23 Neomycin sulfate - gramicidin-_____ ophthalmic solution; neomycin sulfate-gramicidin-_____ ophthalmic suspension (the blanks being filled in with the established name(s) of the other active ingredient(s) present in accordance with paragraph (a)(1) of this section).
148i.24 Neomycin sulfate-gramicidin-hydrocortisone-thonzylamine hydrochloride-thonzonium bromide otic solution.
148i.25 Neomycin sulfate-gramicidin-triamcinolone acetonide loation; neomycin sulfate-gramicidin-fiudrocortisone acetate lotion.
148i.26 Neomycin sulfate-gramicidin ointment; neomycin sulfate-gramicidin-triamcinolone acetonide ointment; neomycin sulfate-gramicidin-fiudrocortisone acetate ointment.
148i.27 Neomycin sulfate-gramicidin-triamcinolone acetonide cream.
148i.28 [Reserved]
148i.29 Neomycin sulfate-nystatin tablets.

AUTHORITY: The provisions of this Part 148i issued under sec. 507, 59 Stat. 463, as amended 76 Stat. 785, 786, 787; 21 U.S.C.A. 357.

§ 148i.1 Neomycin sulfate.

(a) *Requirements for certification*—(1) *Standards of identity, strength, quality, and purity.* Neomycin sulfate is the sulfate salt of a kind of neomycin or a mixture of two or more such salts. It is so purified and dried that:

(i) It has a potency of not less than 600 micrograms of neomycin per milligram, calculated on an anhydrous basis.

(ii) It is sterile.

(iii) It is nonpyrogenic.

(iv) It is nontoxic.

(v) Its moisture content is not more than 8.0 percent.

(vi) Its pH in an aqueous solution containing 33 milligrams per milliliter is not less than 5.0 and not more than 7.5.

(vii) It exhibits absorption maxima, within ±2 mμ, at 232 mμ and 278 mμ when dissolved in sulfuric acid, and the ratio of the absorption peak at 232 mμ ±2 mμ and 278 mμ ±2 mμ, $\frac{A278}{A232}$, is not less than 1.20 and not more than 1.50.

(2) *Packaging.* In addition to the requirements of § 148.2 of this chapter, if it is packaged for dispensing and is intended for intramuscular, intraperitoneal, or topical use, each immediate container shall contain 0.35, 3.5 or 7.0 grams of neomycin.

(3) *Labeling.* In addition to the requirements of § 148.3 of this chapter, if the drug is packaged for dispensing its labeling shall bear adequate warnings for its intramuscular or intraperitoneal use for hospitalized patients only, so as to provide constant supervision by a physician. The labeling shall bear the statement "Refrigerate solution." Its expiration date is 12 months.

(4) *Request for certification; samples.* In addition to the requirements of § 148.4 of this chapter, each such request shall contain:

(i) Results of tests and assays on the batch for potency, sterility, pyrogens, toxicity, moisture, pH, and identity.

(ii) Samples required:

(*a*) If the batch is packaged for repacking or for use in the manufacture of another drug:

(*1*) For all tests except sterility: 10 packages, each containing approximately 300 milligrams.

(*2*) For sterility testing: 10 packages, each containing approximately 500 milligrams.

(*b*) If the batch is packaged for dispensing:

(*1*) For all tests except sterility: A minimum of 10 immediate containers.

(*2*) For sterility testing: 10 immediate containers.

(5) *Fees.* $5.00 for each container submitted in accordance with subparagraph (4)(ii) (*a*)(*1*) and (*b*)(1) of this paragraph; $10.00 for all samples submitted in accordance with subparagraph (4)(ii) (*a*)(*2*) and (*b*)(2) of this paragraph.

(b) *Tests and methods of assay*—(1) *Potency.* Use either of the following methods:

(i) *Plate assay using Staphylococcus epidermidis (ATCC 12228)—(a) Cylinders (cups).* Use cylinders described in § 141a.1(a) of this chapter.

(*b*) *Culture media.* Using ingredients that conform to the standards prescribed by the U.S.P. or N.F.:

(*1*) Make nutrient agar for carrying the test organism as follows:

Peptone	6.0 gm.
Pancreatic digest of casein	4.0 gm.
Yeast extract	3.0 gm.
Beef extract	1.5 gm.
Dextrose	1.0 gm.
Agar	15.0 gm.
Distilled water q.s.	1,000.0 ml.

pH 6.5 to 6.6 after sterilization.

(*2*) Make nutrient agar for the base and seed layers as described in (*b*)(*1*) of this subdivision, except that its pH after sterilization is 7.8 to 8.0.

In lieu of preparing the media from the individual ingredients specified in (*b*)

of this subdivision, they may be made from a dehydrated mixture that, when reconstituted with distilled water, has the same composition as such media. Minor modification of the individual ingredients specified in (*b*) of this subdivision are permissible if the resulting media possess growth-promoting properties at least equal to the media described.

(*c*) *Working standard.* Dry a portion of the working standard for 3 hours at 60° C. and a pressure of 5 millimeters or less. Determine the dry weight, and dissolve in sufficient 0.1*M* potassium phosphate buffer, pH 8.0, to give a stock solution of convenient concentration. When stored under refrigeration, the stock solution may be used for a period not exceeding 2 weeks.

(*d*) *Preparation of sample.* Dissolve an accurately weighed sample in sufficient 0.1*M* potassium phosphate buffer, pH 8.0, to give a stock solution of convenient concentration; and also, if it is packaged for dispensing, reconstitute as directed in the labeling, remove an accurately measured representative portion with a suitable syringe fitted with a 22-gage needle; and dilute with sufficient 0.1*M* potassium phosphate buffer, pH 8.0, to give a stock solution of convenient concentration. Further dilute the stock solution with sufficient 0.1*M* potassium phosphate buffer, pH 8.0, to give a reference concentration of 1.0 microgram of neomycin per milliliter (estimated).

(*e*) *Preparation of test organism.* The test organism is *Staphylococcus epidermidis* (ATCC 12228), which is maintained on slants of nutrient agar described in (*b*)(*1*) of this subdivision. Using 3 milliliters of U.S.P. saline T.S., wash the organism from the nutrient agar slant (which has been incubated for 24 hours at 32° C.–35° C.) onto a large nutrient agar surface such as that provided by a Roux bottle containing 300 milliliters of nutrient agar. Incubate for 24 hours at 32° C.–35° C. Wash the resulting growth from the nutrient surface, using 50 milliliters of sterile U.S.P. saline T.S. Adjust the volume of the suspension so that a 1:14 dilution will give 25 percent light transmission when measured with a suitable photoelectric colorimeter having a 580 mμ filter and a 13-millimeter diameter test tube as an absorption cell. By the use of test plates, determine the appropriate inoculum of the adjusted suspension (usually 0.1 milliliter) to be inoculated to each 100 milliliters of seed layer agar in order to obtain satisfactory zones of inhibition. The suspension may be used for 1 week if stored under refrigeration.

(*f*) *Preparation of plates.* Add 21 milliliters of the agar prepared as described in (*b*)(*2*) of this subdivision to each Petri dish (20 millimeters x 100 millimeters). Distribute the agar evenly in the plates and allow to harden on a level surface. Accurately measure a sufficient quantity of the nutrient agar, cool to 48° C., and add the appropriate inoculum of the adjusted suspension, prepared as described in (*e*) of this subdivision. Swirl the inoculated nutrient agar to obtain a homogeneous suspension, and add 4 milliliters to each of the plates containing the 21 milliliters of uninoculated nutrient agar. Tilt the plates back and forth to spread the inoculated nutrient agar evenly, and allow to harden on a level surface. After the agar has hardened, place six cylinders described in (*a*) of this subdivision on the inoculated agar surface so that they are at approximately 60° intervals on a 2.8-centimeter radius. Use the plates the same day they are prepared.

(*g*) *Standard curve.* Using the stock solution of the working standard prepared as described in (*c*) of this subdivision, prepare solutions in 0.1*M* potassium phosphate buffer pH 8.0 of the following concentrations: 0.64, 0.8, 1.0, 1.25, 1.56 micrograms of neomycin per milliliter. The 1.0 microgram per milliliter concentration is the reference concentration of the assay. Use a total of 12 plates, three plates for each solution except the reference point solution which is included on each plate. On each of the three plates, fill three cylinders with the reference point solution and the other three cylinders with the concentrations under test. Thus, there will be 36 reference point determinations and nine determinations for each of the other points on the curve. After the plates have incubated, read the diameters of the circles of inhibition. Average the readings of the reference point concentration and the readings of the point tested for each set of three plates and average also all 36 readings of the reference point concentration. The average of the 36 readings of the reference point concentration is the correction point of the curve. Correct the average value obtained for each point to the figure it would be if the reference point reading for that set of three plates were the same as the correction point. Thus, if in correcting the 0.8-microgram concentration, the average of the 36 readings of the 1.0 microgram per milliliter (reference point) concentration is 16.5 millimeters and the average of the 1.0 microgram per milliliter concentration of the set of three plates (the 0.8 microgram per milliliter set) is 16.3 millimeters, the correction is +0.2 millimeter. If the average readings of the 0.8 microgram per milliliter concentration of these same three plates is 15.9 millimeters, the corrected value is then 16.1 millimeters. Plot these corrected values, including the average of the 1.0 microgram per milliliter concentration, on 2-cycle semilog paper, using the concentration in micrograms per milliliter as the ordinate (the logarithmic scale) and the diameter of the zone of inhibition as the abscissa. Draw the standard curve through these points either by inspection or by means of the following equations:

$$L=\frac{3a+2b+c-e}{5},$$

$$H=\frac{3e+2d+c-a}{5},$$

where:

L = Calculated zone diameter for the lowest concentration of the standard curve;

H = Calculated zone diameter for the highest concentration of the standard curve;

c = Average zone diameter of 36 readings of the reference point standard solution;

a, b, d, e = Corrected average values for the other standard solutions, lowest to highest concentrations, respectively.

(*h*) *Assay procedure.* Use three plates for each sample. Fill three cylinders on each plate with the standard and three cylinders with the sample, which has been diluted to the reference concentration, alternating standard and sample. Incubate the plates for 16 hours to 18 hours at 32° C.–35° C., and then measure the diameter of each zone of inhibition. To estimate the potency of the sample, average the zone readings of the standard and the zone readings of the sample on the three plates used. If the sample gives a larger zone size than the average of the standard, add the difference between them to the reference point zone of the standard curve. If the average value is lower than the standard value, subtract the difference between them from the reference point value on the curve. From the curve, read the potencies corresponding to these corrected value of zone sizes.

(ii) *Plate assay using Staphylococcus aureus (ATCC 6538P).* Proceed as directed in subdivision (i) of this subparagraph, except that the reference concentration of the sample under test is 10.0 micrograms of neomycin per milliliter; the concentrations of the standard curve solutions are 6.4, 8.0, 10.0, 12.5, 15.6 micrograms of neomycin per milliliter; and the suspension of the test organism, *Staphylococcus aureus* (ATCC 6538P), is adjusted so that a 1:19 dilution will give 25 percent light transmission and the usual inoculum for each 100 milliliters of agar for the seed layer is 0.2 milliliter of the adjusted suspension.

If it is packaged for dispensing, its content of neomycin is not less than 90 percent and not more than 120 percent of the number of milligrams of neomycin that it is represented to contain.

(2) *Sterility.* Using 500 milligrams from each container tested, proceed as directed in § 141a.2 of this chapter, except that neither penicillinase nor the control tube is used in the test for bacteria.

(3) *Pyrogens.* Proceed as directed in § 141a.3 of this chapter, using a test dose of 1.0 milliliter per kilogram of a solution containing 10 milligrams of neomycin per milliliter in pyrogen-free, sterile U.S.P. saline T.S.

(4) *Toxicity.* Proceed as directed in § 141a.4 of this chapter, using 0.5 milliliter of a solution containing 200 micrograms of neomycin per milliliter in sterile U.S.P. saline T.S.

(5) *Moisture.* In an atmosphere of about 10 percent relative humidity, transfer about 100 milligrams of the finely powdered sample to a tared weighing bottle equipped with ground-glass top and stopper. Weigh the bottle and place it in a vacuum oven, tilting the stopper on its side so that there is no closure during the drying period. Dry at a temperature of 60° C. and a pressure of 5 millimeters of mercury or less for 3 hours. At the end of the drying period, fill the vacuum oven with air dried by passing it through a drying agent such as sulfuric acid or silica gel. Replace the stopper and place the weighing bottle in a desiccator over a

desiccating agent such as phosphorus pentoxide or silica gel, allow to cool to room temperature, and reweigh. Calculate the percent loss.

(6) *pH.* Proceed as directed in § 141a.5(b) of this chapter, using a solution containing 33 milligrams of neomycin per milliliter.

(7) *Identity.* Place about 10 milligrams of the sample into a test tube (19 millimeters x 150 millimeters), dissolve with 1 milliliter of water and then add 5 milliliters of a 40 percent volume to volume sulfuric acid solution. Heat in a boiling water bath for 100 minutes. Cool and dilute to a volume of 25 milliliters with water. Use a suitable recording ultraviolet spectrophotometer and 1-centimeter quartz cells. Set the instrument to 100 percent transmission with an 8 percent sulfuric acid solution. Record the spectrum from 220 mμ to 300 mμ. The ratio of the two maximum absorbances $\left(\frac{A278}{A232}\right)$ should be not less than 1.20 and not more than 1.50.

§ 148i.2 Neomycin undecylenate.

(a) *Requirements for certification—*(1) *Standards of identity, strength, quality, and purity.* Neomycin undecylenate is the undecylenate salt of a kind of neomycin or a mixture of two or more such salts. It is so purified and dried that:

(i) It contains not less than 300 micrograms of neomycin per milligram, calculated on an anhydrous basis.

(ii) It contains not less than 600 micrograms of undecylenic acid per milligram, calculated on an anhydrous basis.

(iii) Its moisture content is not more than 5.0 percent.

(iv) The pH of a solution containing 50 milligrams per milliliter in 80 percent methyl alcohol is not less than 6.5 and not more than 7.0.

(v) It gives a positive identity test for neomycin undecylenate.

(2) *Labeling.* It shall be labeled in accordance with the requirements of § 148.3 of this chapter. Its expiration date is 12 months.

(3) *Request for certification; samples.* In addition to the requirements of § 148.4 of this chapter, each such request shall contain:

(i) Results of tests and assays on the batch for potency, moisture, pH, and identity.

(ii) Samples required: 10 packages, each containing approximately 300 milligrams.

(4) Fees. $4.00 for each package in the sample submitted in accordance with subparagraph (3)(ii) of this paragraph.

(b) *Tests and methods of assay—*(1) *Potency—*(i) *Neomycin content.* Proceed as directed in § 148i.1(b)(1)(i), except prepare the sample for assay as follows: Accurately weigh aproximately 500 milligrams of neomycin undecylenate, transfer to a 250-milliliter volumetric flask, add 50 milliliters of chloroform, and mix well. Adjust to volume with 95 percent ethyl alcohol, and mix well. Dilute and aliquot with 0.1*M* potassium phosphate buffer, pH 8.0, to the reference concentration of 1.0 microgram of neomycin per milliliter.

(ii) *Undecylenic acid content—*(a) *Reagents—*(1) *Alcohol.* Use 95 percent ethyl alcohol (aldehyde-free).

(2) *Phenolphthalein indicator.* Dissolve 1 gram of phenolphthalein in 100 milliliters of alcohol.

(3) *Alcoholic sodium hydroxide (about 0.1N).* Prepare alcoholic sodium hydroxide solution as follows: Weigh rapidly about 5 grams of sodium hydroxide pellets, dissolve in 10 milliliters of water, and add sufficient alcohol to make 1,000 milliliters. Allow the solution to stand in a tightly stoppered bottle protected from light for 24 hours. Then quickly decant the clear supernatant liquid into a suitable tight container and store protected from light. Determine the undecylenic acid equivalent of this solution each time an assay is performed.

(b) *Procedure.* Weigh accurately two 100-milligram portions of undecylenic acid (N.F. grade) and place each into separate Erlenmeyer flasks. Also make two accurate weighings of the neomycin undecylenate sample, each consisting of about 120 milligrams, and place each into separate Erlenmeyer flasks. Carefully dissolve each weighing in 10 milliliters of alcohol. Add two drops of phenolphthalein indicator and titrate to the endpoint. Determine the amount of alcoholic sodium hydroxide equivalent to 10 milliliters of alcohol and make this reagent-blank correction for each titration. Determine the undecylenic acid equivalent of the alcoholic sodium hydroxide, and calculate the undecylenic acid content of the neomycin undecylenate sample.

(2) *Moisture.* Proceed as directed in § 141a.5(a) of this chapter.

(3) *pH.* Proceed as directed in § 141a.5(b) of this chapter, except use a solution containing 50 milligrams per milliliter in 80 percent methyl alcohol.

(4) *Identity.* Weigh approximately 1 milligram of neomycin undecylenate and mix thoroughly with 200 milligrams of dried infrared spectrophotometric quality potassium bromide in a small ball mill for about 1 minute. Prepare a potassium bromide disc by transferring the uniform mixture to a die of suitable size. Evacuate gradually while raising the pressure to 3,000 pounds per square inch. Hold at 3,000 pounds per square inch until evacuation is complete and then raise the pressure to 20,000 pounds per square inch. Hold this pressure for 2 or 3 minutes. Using a suitable infrared spectrophotometer, run the spectrum from 2 μ to 16 μ. Use an attenuator if necessary. Characteristic undecylenic acid peak absorbances occur at 7.1 and 11 μ distinguishing neomycin undecylenate from neomycin sulfate.

§ 148i.3 Neomycin sulfate ointment; neomycin sulfate-ointment (the blank being filled in with the established name(s) of the other active ingredient(s) present in accordance with paragraph (a)(1) of this section).

(a) *Requirements for certification—*(1) *Standards of identity, strength, quality, and purity.* Neomycin sulfate ointment contains, in each gram, 3.5 milligrams of neomycin in a suitable and harmless water-soluble or oleaginous ointment base, with or without one or more suitable and harmless dispersants, emollients, and preservatives. The following other drugs may be combined with neomycin sulfate ointment in the indicated amounts, per gram:

(i) If it is for topical use:

(*a*) 0.5 milligram of flurandrenolone; or

(*b*) 0.25 milligram of fluorometholone; or

(*c*) 5.0, 10.0, 15.0, or 25.0 milligrams of hydrocortisone acetate; or

(*d*) 10.0 or 25.0 milligrams of hydrocortisone; or

(*e*) 5.0 milligrams of hydrocortamate hydrochloride; or

(*f*) 1.0, 2.5, or 5.0 milligrams of prednisolone acetate; or

(*g*) 1.0 milligram of triamcinolone acetonide; or

(*h*) 5.0 milligrams of hydrocortisone and 45 milligrams to 55 milligrams of coaltar extract; or

(*i*) 10.0 milligrams of hydrocortisone acetate and 30 milligrams of calcium undecylenate; or

(*j*) 200 milligrams of benzocaine.

(ii) If it is for ophthalmic use:

(*a*) 5.0 milligrams or 15.0 milligrams of hydrocortisone acetate; or

(*b*) 2.5 milligrams of sodium prednisolone phosphate; or

(*c*) 0.5 milligram of sodium dexamethasone phosphate.

(iii) If it is an eye-ear ointment:

(*a*) 1.0 milligram of methylprednisolone; or

(*b*) 1.0 milligram of triamcinolone acetonide; or

(*c*) 5.0 milligrams or 15.0 milligrams of hydrocortisone acetate; or

(*d*) 2.5 milligrams or 5.0 milligrams of prednisolone acetate.

If it is an oleaginous base, its moisture content is not more than 1.0 percent. The neomycin sulfate used conforms to the standards prescribed by § 148i.1(a)(1)(i), (vi), and (vii) and, if for ophthalmic use, paragraph (a)(1)(iv) of that section. Each other substance used, if its name is recognized in the U.S.P. or N.F., conforms to the standards prescribed therefor by such official compendium.

(2) *Labeling.* If it contains a steroid or if it is intended for ophthalmic use, it shall be labeled in accordance with the requirements prescribed by § 148.3 of this chapter, and its expiration date is 12 months. If it does not contain a steroid or it is not intended for ophthalmic use each package shall bear on its label or labeling, as hereinafter indicated, the following:

(i) On the label of the immediate container and on the outside wrapper or container, if any:

(*a*) The batch mark.

(*b*) The name and quantity of each active ingredient contained in the drug.

(*c*) An expiration date that is 12 months after the month during which the batch was certified.

(ii) On the label of the immediate container or other labeling attached to or within the package, adequate direc-

tions under which the layman can use the drug safely and efficaciously.

(3) *Requests for certification; samples.* In addition to the requirements of § 148.4 of this chapter, each such request shall contain:

(i) Results of tests and assays on:

(*a*) The neomycin sulfate used in making the batch for potency, pH, and identity, and, if the ointment is for ophthalmic use, toxicity.

(*b*) The batch for potency and, if the ointment base is oleaginous, moisture.

(ii) Samples required:

(*a*) The neomycin sulfate used in making the batch: 10 packages each containing approximately 300 milligrams.

(*b*) The batch: A minimum of 5 immediate containers.

(*c*) In the case of an initial request for certification, each other ingredient used in making the batch: One package of each containing approximately 5 grams.

(4) *Fees.* $4.00 for each immediate container submitted in accordance with subparagraph (3) (ii) of this paragraph.

(b) *Tests and methods of assay*—(1) *Potency*—(i) *Extraction.* Proceed as directed in § 148i.1(b) (1) of this chapter, except prepare the sample by placing an accurately weighed representative portion of the ointment into a separatory funnel containing 50 milliliters of peroxide-free ether. Shake the sample and ether until homogeneous. Add 25 milliliters of 0.1*M* potassium phosphate buffer, pH 8.0, and shake well. Allow the layers to separate. Remove the buffer layer and repeat the extraction with new portions of the buffer at least three times and any additional times necessary to insure complete extraction of the antibiotic. Combine the extractives and adjust to an appropriate volume to give a stock solution of convenient concentration. Further dilute with 0.1*M* potassium phosphate buffer, pH 8.0, to the proper prescribed reference concentration.

(ii) *Blending.* Proceed as directed in § 148i.1(b) (1), except prepare the sample for assay as follows: Transfer an accurately weighed sample into a high-speed glass blender, add 1.0 milliliter of polysorbate 80 and sufficient 0.1*M* potassium phosphate buffer, pH 8.0, to give a stock solution of convenient concentration. Blend 3 to 5 minutes. Further dilute with 0.1*M* potassium phosphate buffer, pH 8.0, to the proper prescribed reference concentration. The content of neomycin is satisfactory if it is not less than 90 percent and not more than 135 percent of the number of milligrams of neomycin that it is represented to contain.

(2) *Moisture.* If the ointment has an oleaginous base, proceed as directed in § 141a.8(b) of this chapter.

§ 148i.4 Neomycin sulfate-betamethasone cream; neomycin sulfate-sodium dexamethasone phosphate cream; neomycin sulfate-dichlorisone acetate cream; neomycin sulfate-fluocinolone acetonide cream; neomycin sulfate-methylprednisolone acetate cream; neomycin sulfate-triamcinolone acetonide cream.

(a) *Requirements for certification*—(1) *Standards of identity, strength, quality, and purity.* The drug is neomycin sulfate and either betamethasone, dexamethasone phosphate, dichlorisone acetate, fluocinolone acetonide, methylprednisolone acetate, or triamcinolone acetonide, with or without one or more suitable and harmless emollients, perfumes, dispersants, and preservatives, in a suitable and harmless cream base. It contains, in each gram, 3.5 milligrams of neomycin and one of the following:

(i) 2 milligrams of betamethasone; or

(ii) 1 milligram of sodium dexamethasone phosphate; or

(iii) 2.5 milligrams of dichlorisone acetate; or

(iv) 0.25 milligram of fluocinolone acetonide; or

(v) 2.5 milligrams, 5 milligrams, or 10 milligrams of methylprednisolone acetate; or

(vi) 1 milligram of triamcinolone acetonide.

The neomycin sulfate used conforms to the standards prescribed by § 148i.1(a) (1) (i), (vi), and (vii). Each other substance used, if its name is recognized in the U.S.P. or N.F., conforms to the standards prescribed therefor by such official compendium.

(2) *Labeling.* It shall be labeled in accordance with the requirements prescribed by § 148.3 of this chapter. Its expiration date is 12 months.

(3) *Requests for certification; samples.* In addition to the requirements of § 148.4 of this chapter, each such request shall contain:

(i) Results of tests and assays on:

(*a*) The neomycin sulfate used in making the batch for potency, pH, and identity.

(*b*) The batch for potency.

(ii) Samples required:

(*a*) The neomycin sulfate used in making the batch: 10 packages, each containing approximately 300 milligrams.

(*b*) The batch: A minimum of five immediate containers.

(*c*) In case of an initial request for certification, each other ingredient used in making the batch: One package of each containing approximately 5 grams.

(4) *Fees.* $4.00 for each immediate container or package in the samples submitted in accordance with subparagraph (3) (ii) of this paragraph.

(b) *Tests and methods of assay; potency.* Proceed as directed in § 148i.1 (b) (1), except prepare the sample for assay as follows: Transfer an accurately weighed representative portion into a high-speed glass blender. Add 1.0 milliliter of polysorbate 80 and sufficient 0.1*M* potassium phosphate buffer, pH 8.0, to give a stock solution of convenient concentration and blend 3 to 5 minutes. Further dilute with 0.1*M* potassium phosphate buffer, pH 8.0, to the proper prescribed reference concentration. Its neomycin content is satisfactory if it is not less than 90 percent nor more than 135 percent of the number of milligrams of neomycin that it is represented to contain.

§ 148i.5 Neomycin sulfate tablets.

(a) *Requirements for certification*—(1) *Standards of identity, strength, quality, and purity.* Neomycin sulfate tablets are tablets composed of neomycin sulfate with one or more suitable and harmless binders, and with or without one or more suitable and harmless fillers, buffers, lubricants, and colorings. Each tablet contains 150 milligrams, 175 milligrams, or 350 milligrams of neomycin. The moisture content is not more than 10.0 percent. Tablets shall disintegrate within 1 hour. The neomycin sulfate used conforms to the standards prescribed by § 148i.1(a) (1) (i), (iv), (v), (vi), and (vii). Each other substance used, if its name is recognized in the U.S.P. or N.F., conforms to the standards prescribed therefor by such official compendium.

(2) *Labeling.* It shall be labeled in accordance with the requirements of § 148.3 of this chapter. Its expiration date is 12 months.

(3) *Requests for certification; samples.* In addition to the requirements of § 148.4 of this chapter, each such request shall contain:

(i) Results of tests and assays on:

(*a*) The neomycin sulfate used in making the batch for potency, toxicity, moisture, pH, and identity.

(*b*) The batch for potency, moisture, and disintegration time.

(ii) Samples required:

(*a*) The neomycin sulfate used in making the batch: 10 packages, each containing approximately 300 milligrams.

(*b*) The batch:

(*1*) For all tests except disintegration time: Minimum 30 tablets.

(*2*) For disintegration time: Six tablets.

(*c*) In the case of an initial request for certification, each other ingredient used in making the batch: One package of each containing approximately 5 grams.

(4) *Fees.* $0.75 for each tablet submitted in accordance with subparagraph (3) (ii) (*b*) (*1*) of this paragraph; $3.00 for all tablets in the sample submitted in accordance with subparagraph (3) (ii) (*b*) (*2*) of this paragraph; $4.00 for each immediate container submitted in accordance with subparagraph (3) (ii) (*a*) and (*c*) of this paragraph.

(b) *Tests and methods of assay*—(1) *Potency.* Proceed as directed in § 148i.1 (b) (1), except prepare the sample as follows: Place a representative number of tablets into a high-speed glass blender, add a sufficient quantity of 0.1*M* potassium phosphate buffer, pH 8.0, to give a stock solution of convenient concentration. Blend 3 to 5 minutes. Further dilute in 0.1*M* potassium phosphate buffer, pH 8.0, to the proper prescribed reference concentration. Its neomycin content is satisfactory if it contains not less than 90 percent and not more than 125 percent of the number of milligrams of neomycin that it is represented to contain.

(2) *Moisture.* Proceed as directed in § 141a.5(a) of this chapter.

(3) *Disintegration time.* Proceed as directed in § 141a.9(c) of this chapter.

§ 148i.6 Neomycin sulfate-kaolin-pectin oral suspension; neomycin sulfate-kaolin-pectin-_____ oral suspension (the blank being filled in with the established name(s) of the other active ingredient(s) present in accordance with paragraph (a) (1) of this section).

(a) *Requirements for certification*—(1) *Standards of identity, strength, qual-*

ity, and purity. Neomycin sulfate-kaolin-pectin oral suspension is neomycin sulfate, kaolin, and pectin, with or without one or more suitable and harmless dispersants, colorings, flavorings, buffers, and preservatives, in an aqueous vehicle. One or more of the following drugs may be added to neomycin sulfate-kaolin-pectin oral suspension: Methylcellulose, dihydroxyaluminum aminoacetate, succinylsulfathiazole, sulfaguanidine, homatropine methylbromide, hyoscyamine sulfate, atropine sulfate. scopolamine hydrobromide, and phenobarbital. Each milliliter contains 7.0 milligrams of neomycin. Its pH is not less than 4.0 and not more than 6.5. The neomycin sulfate used conforms to the standards prescribed by § 148i.1(a)(1)(i), (iv), (vi), and (vii). Each other substance used, if its name is recognized in the U.S.P. or N.F., conforms to the standards prescribed therefor by such official compendium.

(2) *Labeling.* It shall be labeled in accordance with the requirements of § 148.3 of this chapter. Its expiration date is 12 months.

(3) *Request for certification; samples.* In addition to the requirements of § 148.4 of this chapter, each such request shall contain:

(i) Results of tests and assays on:

(*a*) The neomycin sulfate used in making the batch for potency, toxicity, pH, and identity.

(*b*) The batch for potency and pH.

(ii) Samples required:

(*a*) The neomycin sulfate used in making the batch: 10 packages, each containing approximately 300 milligrams.

(*b*) The batch: Minimum of 5 immediate containers.

(*c*) In case of an initial request for certification, each other ingredient used in making the batch: One package of each containing approximately 5 grams.

(4) *Fees.* $4.00 for each immediate container submitted in accordance with subparagraph (3)(ii) of this paragraph.

(b) *Tests and methods of assay*—(1) *Potency.* Proceed as directed in § 148i.1(b)(1), except to prepare the sample for assay, proceed as follows: Dissolve and dilute an accurately measured representative portion in sufficient 0.1*M* potassium phosphate buffer, pH 8.0, to give a stock solution of convenient concentration. Further dilute in 0.1*M* potassium phosphate buffer, pH 8.0, to the proper prescribed reference concentration. Its content of neomycin is satisfactory if it contains not less than 90 percent and not more than 125 percent of the number of milligrams of neomycin that it is represented to contain.

(2) *pH.* Proceed as directed in § 141a.5(b) of this chapter, using the undiluted suspension.

§ 148i.7 Neomycin sulfate-_____ nasal suspension; neomycin sulfate-_____ nasal solution (the blanks being filled in with the established name(s) of the other active ingredient(s) present in accordance with paragraph (a)(1) of this section).

(a) *Requirements for certification*—(1) *Standards of identity, strength, quality, and purity.* The drug is a suspension or solution containing, in each milliliter, 3.5 milligrams of neomycin and the following other active ingredients, in a suitable and harmless vehicle:

(i) 5.0 milligrams or 15.0 milligrams of hydrocortisone acetate and 2.5 milligrams of phenylephrine hydrocholoride; or

(ii) 0.5 milligram or 1.0 milligram of prednisolone acetate and 2.5 milligrams of phenylephrine hydrochloride; or

(iii) 0.1 milligram of fludrocortisone, 2.5 milligrams of phenylephrine hydrochloride, and 7.5 milligrams of phenylpropanolamine hydrochloride; or

(iv) 1.0 milligram of hydrocortisone, 2.5 milligrams of phenylephrine hydrochloride, and 7.5 milligrams of phenylpropanolamine hydrochloride; or

(v) 1.04 milligrams of sodium prednisolone phosphate, 2.5 milligrams of phenylephrine hydrochloride, and 7.5 milligrams of phenylpropanolamine hydrochloride; or

(vi) 0.5 milligram of prednisolone trimethylacetate and 0.5 milligram of xylometazoline hydrochloride.

It may also contain one or more suitable and harmless buffers, colorings, dispersants, flavorings, and preservatives. Its pH is not less than 5.5 and not more than 6.5, except that if it is the drug described in subdivision (iv) of this subparagraph, its pH is not less than 2.8 nor more than 6.5. The neomycin sulfate used conforms to the standards prescribed by § 148i.1(a)(1)(i), (iv), (vi), and (vii). Each other substance used, if its name is recognized in the U.S.P. or N.F., conforms to the standards prescribed therefor by such official compendium.

(2) *Labeling.* It shall be labeled in accordance with the requirements of § 148.3 of this chapter. Its expiration date is 12 months.

(3) *Request for certification; samples.* In addition to the requirements of § 148.4 of this chapter, each such request shall contain:

(i) Results of tests and assays on:

(*a*) The neomycin sulfate used in making the batch for potency, toxicity, pH, and identity.

(*b*) The batch for potency and pH.

(ii) Samples required:

(*a*) The neomycin sulfate used in making the batch: 10 packages, each containing approximately 300 milligrams.

(*b*) The batch: A minimum of 5 immediate containers.

(*c*) In case of an initial request for certification, each other ingredient used in making the batch: One package of each containing approximately 5 grams.

(4) *Fees.* $4.00 for each immediate container submitted in accordance with subparagraph (3)(ii) of this paragraph.

(b) *Tests and methods of assay*—(1) *Potency.* Proceed as directed in § 148i.1(b)(1), except dilute volumetrically an accurately measured representative portion in sufficient 0.1*M* potassium phosphate buffer, pH 8.0, to give a stock solution of convenient concentration. Further dilute with 0.1*M* potassium phosphate buffer, pH 8.0, to the proper prescribed reference concentration. Its content of neomycin is satisfactory if it contains not less than 90 percent and not more than 130 percent of the number of milligrams of neomycin that it is represented to contain.

(2) *pH.* Proceed as directed in § 141a.5(b) of this chapter, using the undiluted sample.

§ 148i.8 Neomycin sulfate-sodium propionate otic solution; neomycin sulfate-sodium proprionate-prednisolone acetate otic solution.

(a) *Requirements for certification*—(1) *Standards of identity, strength, quality, and purity.* Neomycin sulfate-sodium propionate otic solution is a solution containing, in each milliliter, 3.5 milligrams of neomycin and 50 milligrams of sodium propionate, in a suitable and harmless vehicle. Neomycin sulfate-sodium propionate-prednisolone acetate otic solution is a solution containing, in each milliliter, 3.5 milligrams of neomycin, 50 milligrams of sodium propionate, and 5 milligrams of prednisolone acetate, in a suitable and harmless vehicle. The preparations may also contain suitable and harmless dispersants, buffers, perfumes, and preservatives. They are sterile. Their pH is not less than 5.5 and not more than 7.0. The neomycin sulfate used conforms to the standards prescribed by § 148i.(a)(1)(i), (vi), and (vii). Each other substance used, if its name is recognized in the U.S.P. or N.F., conforms to the standards prescribed therefor by such official compendium.

(2) *Labeling.* It shall be labeled in accordance with the requirements of § 148.3 of this chapter. Its expiration date is 12 months.

(3) *Requests for certification; samples.* In addition to the requirements of § 148.4 of this chapter, each such request shall contain:

(i) Results of tests and assays on:

(*a*) The neomycin sulfate used in making the batch for potency, pH, and identity.

(*b*) The batch for potency, sterility, and pH.

(ii) Samples required:

(*a*) The neomycin sulfate used in making the batch: 10 packages, each containing approximately 300 milligrams.

(*b*) The batch:

(*1*) For all tests except sterility: A minimum of five immediate containers.

(*2*) For sterility testing: 10 immediate containers.

(*c*) In case of an initial request for certification, each other ingredient used in making the batch: One package of each containing approximately 5 grams.

(4) *Fees.* $4.00 for each sample submitted in accordance with subparagraph (3)(ii) (*a*), (*b*)(*1*), and (*c*) of this paragraph; $10.00 for all containers in the sample submitted in accordance with subparagraph (3)(ii)(*b*)(*2*) of this paragraph.

(b) *Tests and methods of assay*—(1) *Potency.* Proceed as directed in § 148i.1(b)(1), except dilute an accurately measured representative portion in sufficient 0.1*M* potassium phosphate buffer, pH 8.0, to give a stock solution of convenient concentration. Further dilute an aliquot with 0.1*M* potassium phosphate buffer, pH 8.0, to the proper prescribed reference concentration. Its content of neomycin

is satisfactory if it contains not less than 90 percent and not more than 125 percent of the number of milligrams of neomycin that it is represented to contain.

(2) *Sterility.* Using 0.25 milliliter from each container, proceed as directed in § 141a.2 of this chapter, except that neither penicillinase nor the control tube is used in the test for bacteria.

(3) *pH.* Proceed as directed in § 141a.5(b) of this chapter, using either the undiluted sample or, if the drug contains less than 10 percent water, a 1:1 dilution of the sample with distilled water.

§ 148i.9 Neomycin sulfate-_____ ophthalmic suspension; neomycin sulfate-_____ ophthalmic solution (the blanks being filled in with the established name(s) of the other active ingredient(s) present in accordance with paragraph (a)(1) of this section).

(a) *Requirements for certification—*(1) *Standards of identity, strength, quality, and purity.* The drug is a suspension or a solution containing, in each milliliter, 3.5 milligrams of neomycin and the following other active ingredients in a suitable and harmless vehicle:

(i) 15 milligrams of cortisone acetate; or

(ii) 5 milligrams or 25 milligrams of hydrocortisone acetate; or

(iii) 2 milligrams of prednisolone and 1.2 milligrams of phenylephrine hydrochloride; or

(iv) 1 milligram or 2 milligrams of prednisolone; or

(v) 1 milligram of sodium dexamethasone phosphate.

It may also contain one or more suitable and harmless buffers, dispersants, and preservatives. It is sterile. Its pH is not less than 6.0 and not more than 8.0. The neomycin sulfate used conforms to the standards prescribed by § 148i.1(a)(1) (i), (iv), (vi), and (vii). Each other substance used, if its name recognized in the U.S.P. or N.F., conforms to the standards prescribed therefor by such official compendium.

(2) *Labeling.* It shall be labeled in accordance with the requirements of § 148.3 of this chapter. Its expiration date is 12 months.

(3) *Request for certification; samples.* In addition to the requirements of § 148.4 of this chapter, each such request shall contain:

(i) Results of tests and assays on:

(*a*) The neomycin sulfate used in making the batch for potency, toxicity, pH, and identity.

(*b*) The batch for potency, sterility, and pH.

(ii) Samples required:

(*a*) The neomycin sulfate used in making the batch: 10 containers, each containing approximately 300 milligrams.

(*b*) The batch:

(*1*) For all tests except sterility: A minimum of 5 immediate containers.

(2) For sterility testing: 10 immediate containers.

(*c*) In case of an initial request for certification, each other ingredient used in making the batch: One package of each containing approximately 5 grams.

(4) *Fees.* $4.00 for each container submitted in accordance with subparagraph (3)(ii) (*a*), (*b*)(*1*), and (*c*) of this paragraph; $10.00 for all containers submitted in accordance with subparagraph (3)(ii)(*b*)(2) of this paragraph.

(b) *Tests and methods of assay—*(1) *Potency.* Proceed as directed in § 148i.8(b)(1). Its neomycin content is satisfactory if it contains not less than 90 percent and not more than 130 percent of the number of milligrams of neomycin that it is represented to contain.

(2) *Sterility.* Proceed as directed in § 141a.2 of this chapter, using 0.25 milliliter from each container, except that neither penicillinase nor the control tube is used in the test for bacteria.

(3) *pH.* Proceed as directed in § 141a.5(b) of this chapter, using the undiluted sample.

§ 148i.10 Neomycin sulfate-_____ lotion (the blank being filled in with the established name(s) of the other active ingredient(s) present in accordance with paragraph (a)(1) of this section).

(a) *Requirements for certification—*(1) *Standards of identity, strength, quality, and purity.* The drug is a suspension containing, in each milliliter, 3.5 milligrams of neomycin and the following other active ingredients in a suitable and harmless vehicle:

(i) 10 milligrams of diperodon hydrochloride and 7.5 milligrams of aluminum dihydroxy allantoinate; or

(ii) 5 milligrams or 10 milligrams of hydrocortisone acetate; or

(iii) 5 milligrams, 10 milligrams, or 20 milligrams of hydrocortisone; or

(iv) 1 milligram, 2.5 milligrams, or 5 milligrams of prednisolone acetate; or

(v) 5.0 milligrams of sodium prednisolone phosphate.

It may also contain one or more suitable and harmless dispersants, emollients, and preservatives. The neomycin sulfate used conforms to the standards prescribed by § 148i.1(a)(1) (i), (vi), and (vii). Each other substance used, if its name is recognized in the U.S.P. or N.F., conforms to the standards prescribed therefor by such official compendium.

(2) *Labeling.* If it contains a corticosteroid, it shall be labeled in accordance with the requirements prescribed by § 148.3 of this chapter and its expiration date is 12 months. If it does not contain a corticosteroid, each package shall bear, on its label or labeling, as hereinafter indicated, the following:

(i) On the label of the immediate container and on the outside wrapper or container, if any:

(*a*) The batch mark.

(*b*) The name and quantity of each active ingredient contained in the drug.

(*c*) An expiration date that is 12 months after the month during which the batch was certified.

(ii) On the label of the immediate container or other labeling attached to or within the package, adequate directions under which the layman can use the drug safely and efficaciously.

(3) *Requests for certification; samples.* In addition to the requirements of § 148.4 of this chapter, each such request shall contain:

(i) Results of tests and assays on:

(*a*) The neomycin sulfate used in making the batch for potency, pH, and identity.

(*b*) The batch for potency.

(ii) Samples required:

(*a*) The neomycin sulfate used in making the batch: 10 packages, each containing approximately 300 milligrams.

(*b*) The batch: A minimum of five immediate containers.

(*c*) In case of an initial request for certification, each other ingredient used in making the batch: One package of each containing approximately 5 grams.

(4) *Fees.* $4.00 for each container submitted in accordance with subparagraph (3)(ii) of this paragraph.

(b) *Tests and methods of assay; potency.* Proceed as directed in § 148i.1(b)(1), except prepare the sample for assay as follows: Place an accurately measured representative portion into a high-speed glass blender with sufficient 0.1*M* potassium phosphate buffer, pH 8, to give a stock solution of convenient concentration. Blend 3 to 5 minutes. Make further dilutions with 0.1*M* potassium phosphate buffer, pH 8, to the proper prescribed reference concentration. Its content of neomycin is satisfactory if it is not less than 90 percent and not more than 130 percent of the number of milligrams of neomycin that it is represented to contain.

§ 148i.11 Neomycin sulfate-thihexinol methylbromide-polycarbophil tablets.

Neomycin sulfate-thihexinol methylbromide-polycarbophil tablets conform to all requirements and are subject to all procedures prescribed by § 148i.5 for neomycin sulfate tablets, except that:

(a) Each tablet contains 150 milligrams of neomycin, 15 milligrams of thihexinol methylbromide, and 400 milligrams of polycarbophil.

(b) The tablets shall disintegrate within 1 hour.

§ 148i.12 Neomycin sulfate-hydrocortisone acetate suppositories.

(a) *Requirements for certification—*(1) *Standards of identity, strength, quality, and purity.* Neomycin sulfate-hydrocortisone acetate suppositories contain, in each suppository, 10.5 milligrams of neomycin and 15 milligrams of hydrocortisone acetate, in a suitable and harmless base, with one or more suitable and harmless surfactants, emollients, protectants, binders, and fillers. The moisture content is not more than 2.5 percent. The neomycin sulfate used conforms to the standards prescribed by § 148i.1(a)(1) (i), (v), (vi), and (vii). Each other substance used, if its name is recognized in the U.S.P. or N.F., conforms to the standards prescribed therefor by such official compendium.

(2) *Labeling.* It shall be labeled in accordance with the requirements of § 148.3 of this chapter. The expiration date is 12 months.

(3) *Requests for certification; samples.* In addition to the requirements of § 148.4 of this chapter, each such request shall contain:

(i) Results of tests and assays on:

(*a*) The neomycin sulfate used in making the batch for potency, moisture, pH, and identity.

(*b*) The batch for potency and moisture.

(ii) Samples required:

(*a*) The neomycin sulfate used in making the batch: 10 packages, each containing approximately 300 milligrams.

(*b*) The batch: A minimum of 30 suppositories.

(*c*) In case of an initial request for certification, each other ingredient used in making the batch: One package of each containing approximately 5 grams.

(4) *Fees.* $0.75 for each suppository in the sample submitted in accordance with subparagraph (3)(ii)(*b*) of this paragraph; $4.00 for each package in the sample submitted in accordance with subparagraph (3)(ii) (*a*) and (*c*) of this paragraph.

(b) *Tests and methods of assay*—(1) *Potency.* Proceed as directed in § 148i.1 (b)(1) of this chapter, except prepare the sample by blending a representative number of suppositories in a high-speed glass blender with 1.0 milliliter of polysorbate 80 and sufficient 0.1*M* potassium phosphate buffer, pH 8.0, to give a stock solution of convenient concentration. Further dilute in 0.1*M* potassium phosphate buffer, pH 8.0, to the proper prescribed reference concentration. The content of neomycin is satisfactory if it contains not less than 90 percent and not more than 130 percent of the number of milligrams of neomycin that it is represented to contain.

(2) *Moisture.* Proceed as directed in § 141a.8(b) of this chapter.

§ 148i.13 [Reserved]

§ 148i.14 Neomycin sulfate-triamcinolone acetonide topical aerosol; neomycin sulfate-dexamethasone topical aerosol.

(a) *Requirements for certification*—(1) *Standards of identity, strength, quality, and purity.* The drug is neomycin sulfate and triamcinolone acetonide or dexamethasone, packaged in a pressurized container with a suitable and harmless vehicle and inert propellants. It contains, in each container, the following:

(i) 26.25 milligrams of neomycin and 7.5 milligrams of triamcinolone acetonide; or

(ii) 52.5 milligrams of neomycin and 15 milligrams of triamcinolone acetonide; or

(iii) 35 milligrams of neomycin and 10 milligrams of dexamethasone.

It may contain one or more suitable and harmless emollients, dispersants, and preservatives. The neomycin sulfate used conforms to the standards prescribed by § 148i.1(a)(1) (i), (vi), and (vii). Each other ingredient used, if its name is recognized in the U.S.P. or N.F., conforms to the standards prescribed therefor by such official compendium.

(2) *Labeling.* It shall be labeled in accordance with the requirements of § 148.3 of this chapter. Its expiration date is 12 months.

(3) *Requests for certification; samples.* In addition to the requirements of § 148.4 of this chapter, each such request shall contain:

(i) Results of tests and assay on:

(*a*) The neomycin sulfate used in making the batch for potency, pH, and identity.

(*b*) The batch for potency.

(ii) Samples required:

(*a*) The neomycin sulfate used in making the batch: 10 packages, each containing 300 milligrams.

(*b*) The batch: A minimum of 5 immediate containers.

(*c*) In case of an initial request for certification, each other ingredient used in making the batch: One package of each containing approximately 5 grams.

(4) *Fees.* $4.00 for each immediate container or package submitted in accordance with subparagraph (3)(ii) of this paragraph.

(b) *Tests and methods of assay; potency.* Proceed as directed in § 148i.1 (b)(1), except prepare the sample for assay as follows: Spray the entire contents of the well-shaken sample into a suitable tared beaker. Place in a vaccum desiccator, evacuate, and allow to stand at room temperature for 16 to 18 hours. After the gas has volatilized, accurately weigh the beaker and contents, and determine the weight of the material in the beaker. Prepare the material for assay by either of the following methods:

(1) Blend an accurately weighed representative portion for 3 to 5 minutes in a high-speed glass blender, with 1.0 milliliter of polysorbate 80 and sufficient 0.1*M* potassium phosphate buffer, pH 8.0, to give a stock solution of convenient concentration. Further dilute with 0.1*M* potassium phosphate buffer, pH 8.0, to the proper prescribed reference concentration.

(2) Quantitatively transfer either an accurately weighed portion of the contents, or the entire contents, from the beaker into a suitable volumetric flask to give a stock solution of convenient concentration. Dilute to volume with 0.1*M* potassium phosphate buffer, pH 8.0. Further dilute with 0.1*M* potassium phosphate buffer, pH 8.0, to the proper prescribed reference concentration.

The content of neomycin is satisfactory if it is not less than 90 percent and not more than 130 percent of the number of milligrams of neomycin that it is represented to contain.

§ 148i.15 Neomycin sulfate-polymyxin B sulfate---------- ophthalmic suspension; neomycin sulfate-polymyxin B sulfate---------- ophthalmic solution (the blanks being filled in with the established name(s) of the other active ingredient(s) present in accordance with paragraph (a)(1) of this section).

(a) *Requirements for certification*—(1) *Standards of identity, strength, quality, and purity.* The drug is a solution or suspension in a suitable and harmless aqueous vehicle containing, in each milliliter, neomycin sulfate, polymyxin B sulfate, and other active ingredients in the following amounts:

(i) 3.5 milligrams of neomycin, 16,250 units of polymyxin B, and 1.25 milligrams of phenylephrine hydrochloride; or

(ii) 3.5 milligrams of neomycin, 16,250 units of polymyxin B, and either 5 milligrams or 15 milligrams of hydrocortisone acetate; or

(iii) 5 milligrams of neomycin, 20,000 units of polymyxin B, and 1.25 milligrams of phenylephrine hydrochloride; or

(iv) 5 milligrams of neomycin, 15,000 units of polymyxin B, and 2.5 milligrams of hydrocortisone.

It may contain one or more suitable and harmless irrigants, dispersants, buffers, and preservatives. It is sterile. Its pH is not less than 5.0 and not more than 7.0. The neomycin sulfate used conforms to the standards prescribed by § 148i.1(a)(1) (i), (iv), (vi), and (vii). The polymyxin B sulfate used conforms to the standards prescribed by § 148p.1(a)(1) (i), (iv), (vi), (vii), and (ix) of this chapter. Each other substance used, if its name is recognized in the U.S.P. or N.F., conforms to the standards prescribed therefor by such official compendium.

(2) *Labeling.* It shall be labeled in accordance with the requirements of § 148.3 of this chapter. Its expiration date is 12 months.

(3) *Requests for certification; samples.* In addition to the requirements of § 148.4 of this chapter, each such request shall contain:

(i) Results of tests and assays on:

(*a*) The neomycin sulfate used in making the batch for potency, toxicity, pH, and identity.

(*b*) The polymyxin B sulfate used in making the batch for potency, toxicity, pH, residue on ignition, and identity.

(*c*) The batch for neomycin content, polymyxin content, sterility, and pH.

(ii) Samples required:

(*a*) The neomycin sulfate used in making the batch: 10 packages, each containng approximately 300 milligrams.

(*b*) The polymyxin B sulfate used in making the batch: 10 packages, each containing approximately 300 milligrams.

(*c*) The batch for:

(*1*) All tests except sterility: A minimum of 6 immediate containers.

(*2*) For sterility testing: 10 immediate containers.

(*d*) In case of an initial request for certification, each other ingredient used in making the batch: One package of each containing approximately 5 grams.

(4) *Fees.* $4.00 for each immediate container or package in the samples submitted in accordance with subparagraphs (3)(ii) (*a*), (*b*), and (*d*) of this paragraph; $5.00 for each immediate container submitted in accordance with subparagraph (3)(ii)(*c*)(*1*) of this paragraph; $10.00 for all immediate containers in the sample submitted in accordance with subparagraph (3)(ii)(*c*)(*2*) of this paragraph.

(b) *Tests and methods of assay*—(1) *Potency*—(i) *Neomycin content.* Proceed as directed in § 148i.1(b)(1) except prepare the sample as follows: Remove an accurately measured representative

portion of the sample with a suitable syringe, place into an appropriate volumetric flask to yield a convenient stock solution. Dilute to volume with 0.1*M* potassium phosphate buffer, pH 8.0. Further dilute with 0.1*M* potassium phosphate buffer, pH 8.0, to the proper prescribed reference concentration. Its content of neomycin is satisfactory if it is not less than 90 percent and not more than 125 percent of the number of milligrams of neomycin that it is represented to contain.

(ii) *Polymyxin content.* Remove an accurately measured representative portion with a suitable syringe, dilute to a convenient concentration with 10 percent potassium phosphate buffer, pH 6.0. Further dilute to a concentration of 10 units of polymyxin per milliliter with 10 percent potassium phosphate buffer, pH 6.0, and proceed as directed in § 148p.1(b)(1) of this chapter, except add to each concentration of the polymyxin standard curve a quantity of neomycin to yield the same concentration of neomycin as that present when the sample is diluted to contain 10 units of polymyxin per milliliter. Its content of polymyxin is satisfactory if it is not less than 90 percent and not more than 125 percent of the number of units of polymyxin that it is represented to contain.

(2) *Sterility.* Use 0.25 milliliter from each container tested, and proceed as directed in § 141a.2 of this chapter, except that neither penicillinase nor a control tube is used in the test for bacteria.

(3) *pH.* Proceed as directed in § 141a.5(b) of this chapter, using the undiluted sample.

§ 148i.16 Neomycin sulfate-polymyxin B sulfate ointment.

(a) *Requirements for certification—*(1) *Standards of identity, strength, quality, and purity.* Neomycin sulfate-polymyxin B sulfate ointment is an ointment containing, in each gram, 3.5 milligrams of neomycin and 5,000 units of polymyxin B with suitable and harmless emollients, dispersants, and preservatives in a suitable and harmless water-miscible base. The neomycin sulfate used conforms to the standards prescribed by § 148i.1(a)(1) (i), (vi), and (vii). The polymyxin B sulfate used conforms to the standards prescribed by § 148p.1(a)(1) (i), (vi), (vii), and (ix) of this chapter. Each other substance used, if its name is recognized in the U.S.P. or N.F., conforms to the standards prescribed therefor by such official compendium.

(2) *Labeling.* Each package shall bear on its label or labeling, as hereinafter indicated, the following:

(i) On the label of the immediate container and on the outside wrapper or container, if any:

(*a*) The batch mark.

(*b*) The name and quantity of each active ingredient contained in the drug.

(*c*) An expiration date that is 12 months after the month during which the batch was certified.

(ii) On the label of the immediate container or other labeling attached to or within the package, adequate directions under which the layman can use the drug safely and efficaciously.

(3) *Requests for certification; samples.* In addition to the requirements of § 148.4 of this chapter, each such request shall contain:

(i) Results of tests and assays on:

(*a*) The neomycin sulfate used in making the bach for potency, pH, and identity.

(*b*) The polymyxin B sulfate used in making the batch for potency, pH, residue on ignition, and identity.

(*c*) The batch for neomycin content and polymyxin content.

(ii) Samples required:

(*a*) The neomycin sulfate used in making the batch: 10 packages, each containing approximately 300 milligrams.

(*b*) The polymyxin B sulfate used in making the batch: 10 packages, each containing approximately 300 milligrams.

(*c*) The batch: A minium of 6 immediate containers.

(*d*) In case of an initial request for certification, each other ingredient used in making the batch: One package of each containing approximately 5 grams.

(4) *Fees.* $4.00 for each package in the samples submitted in accordance with subparagraph (3)(ii) (*a*), (*b*), and (*d*) of this paragraph; $5.00 for each immediate container submitted in accordance with subparagraph (3)(ii)(*c*) of this paragraph.

(b) *Tests and methods of assay—*(1) *Potency—*(i) *Neomycin content.* Proceed as directed in § 148i.3(b)(1)(ii). Its content of neomycin is satisfactory if it is not less than 90 percent and not more than 125 percent of the number of milligrams of neomycin that it is represented to contain.

(ii) *Polymyxin content.* Proceed as directed in § 148p.3(b)(1) of this chapter, except add to each concentration of the polymyxin standard curve a quantity of neomycin to yield the same concentration of neomycin as that present when the sample is diluted to contain 10 units of polymyxin per milliliter. Its content of polymyxin is satisfactory if it is not less than 90 percent and not more than 125 percent of the number of units of polymyxin that it is represented to contain.

§ 148i.17 [Reserved]

§ 148i.18 Neomycin sulfate-polymyxin B sulfate-hydrocortisone otic suspension; neomycin sulfate-polymyxin B sulfate-hydrocortisone-sodium heparin otic suspension.

(a) *Requirements for certification—*(1) *Standards of identity, strength, quality, and purity.* Neomycin sulfate-polymyxin B sulfate-hydrocortisone otic suspension is a suspension containing, in each milliliter, 3.5 milligrams of neomycin, 10,000 units of polymyxin B, and 10 milligrams of hydrocortisone, in a suitable and harmless vehicle. Neomycin sulfate-polymyxin B sulfate-hydrocortisone-sodium heparin otic suspension is a suspension containing, in each milliliter, 20 milligrams of neomycin, 100,000 units of polymyxin B, 5 milligrams of hydrocortisone, and 2,000 units of sodium heparin, in a suitable and harmless vehicle. The preparations may also contain one or more suitable and harmless buffers, dispersants, and preservatives. They are sterile. If the vehicle is aqueous, the pH is not less than 5.5 and not more than 8.5. If the vehicle is nonaqueous, the moisture content is not more than 1.0 percent. The neomycin sulfate used conforms to the standards prescribed by § 148i.1(a)(1) (i), (vi), and (vii). The polymyxin B sulfate used conforms to the standards prescribed by § 148p.1(a)(1), (i), (vi), (vii), and (ix) of this chapter. Each other substance used, if its name is recognized in the U.S.P. or N.F., conforms to the standards prescribed therefor by such official compendium.

(2) *Labeling.* It shall be labeled in accordance with the requirements of § 148.3 of this chapter. Its expiration date is 12 months.

(3) *Requests for certification; samples.* In addition to the requirements of § 148.4 of this chapter, each such request shall contain:

(i) Results of tests and assays on:

(*a*) The neomycin sulfate used in making the batch for potency, pH, and identity.

(*b*) The polymyxin B sulfate used in making the batch for potency, pH, residue on ignition, and identity.

(*c*) The batch, for neomycin content; polymyxin content; sterility; and either pH (if aqueous vehicle), or moisture (if nonaqueous vehicle).

(ii) Samples required:

(*a*) The neomycin sulfate used in making the batch: 10 packages, each containing 300 milligrams.

(*b*) The polymyxin B sulfate used in making the batch: 10 packages, each containing approximately 300 milligrams.

(*c*) The batch:

(*1*) For all tests except sterility: A minimum of six immediate containers.

(*2*) For sterility testing: 10 immediate containers.

(*d*) In case of an initial request for certification, each other ingredient used in making the batch: One package of each containing approximately 5 grams.

(4) *Fees.* $4.00 for each package in the samples submitted in accordance with subparagraph (3)(ii) (*a*), (*b*), and (*d*) of this paragraph; $5.00 for each immediate container submitted in accordance with subparagraph (3)(ii)(*c*)(*1*) of this paragraph; $10.00 for all immediate containers in the sample submitted in accordance with subparagraph (3)(ii)(*c*)(*2*) of this paragraph.

(b) *Tests and methods of assay—*(1) *Potency—*(i) *Neomycin content.* Proceed as directed in § 148i.8(b)(1), except that if the vehicle is nonaqueous prepare the sample for assay as follows: Transfer an accurately measured representative portion to a high-speed glass blender. Add 1.0 milliliter of polysorbate 80 and sufficient 0.1*M* potassium phosphate buffer, pH 8.0, to give a stock solution of convenient concentration. Blend 3 to 5 minutes. Further dilute with 0.1*M* potassium phosphate buffer, pH 8.0, to the proper prescribed reference conceneration. The content of neo-

mycin is satisfactory if it is not less than 90 percent and not more than 125 percent of the number of milligrams of neomycin that it is represented to contain.

(ii) *Polymyxin content.* Proceed as directed in § 148p.1(b)(1) of this chapter, except:

(*a*) Prepare the sample for assay by either of the following methods:

(*1*) If the vehicle is aqueous, dissolve and dilute with 10 percent potassium phosphate buffer, pH 6.0, to the reference concentration of 10 units of polymyxin per milliliter; or

(*2*) If the vehicle is nonaqueous, transfer an accurately measured representative portion to a high-speed glass blender. Add 1.0 milliliter of polysorbate 80 and sufficient 10 percent potassium phosphate buffer, pH 6.0, to give a stock solution of convenient concentration. Blend 3 to 5 minutes. Further dilute with 10 percent potassium phosphate buffer, pH 6.0, to a reference concentration of 10 units of polymyxin per milliliter; and

(*b*) Add to each concentration of the polymyxin standard curve a quantity of neomycin to yield the same concentration of neomycin as that present when the sample is diluted to contain 10 units of polymyxin per milliliter.

Its content of polymyxin is satisfactory if it is not less than 90 percent and not more than 125 percent of the number of units of polymyxin that it is represented to contain.

(2) *pH.* If its vehicle is aqueous, proceed as directed in § 141a.5(b) of this chapter, using the undiluted sample.

(3) *Moisture.* If its vehicle is nonaqueous, proceed as directed in § 141a.8(b) of this chapter.

(4) *Sterility.* Using 0.25 milliliter from each container tested, proceed as directed in § 141a.2 of this chapter, except that neither penicillinase nor the control tube is used in the test for bacteria.

§ 148i.19 Neomycin sulfate-polymyxin B sulfate-acetarsone vaginal suppositories.

(a) *Requirements for certification*—(1) *Standards of identity, strength, quality, and purity.* Neomycin sulfate-polymyxin B sulfate-acetarsone vaginal suppositories are suppositories composed of neomycin sulfate, polymyxin B sulfate, and acetarsone, with one or more suitable and harmless binders, lubricants, and dispersants in a suitable and harmless base. Each suppository contains 3.5 milligrams of neomycin, 20,000 units of polymyxin B, and 250 milligrams of acetarsone. Its moisture content is not more than 3.0 percent. The neomycin sulfate used conforms to the standards prescribed by § 148i.1(a)(1)(i), (v), (vi), and (vii). The polymyxin B sulfate used conforms to the standards prescribed by § 148p.1(a)(1)(i), (v), (vi), (vii), and (ix) of this chapter. Each other substance used, if its name is recognized in the U.S.P. or N.F., conforms to the standards prescribed therefor by such official compendium.

(2) *Labeling.* It shall be labeled in accordance with the requirements of § 148.3 of this chapter. Its expiration date is 12 months.

(3) *Request for certification; samples.* In addition to the requirements of § 148.4 of this chapter, each such request shall contain:

(i) Results of tests and assays on:

(*a*) The neomycin sulfate used in making the batch for potency, moisture, pH, and identity.

(*b*) The polymyxin B sulfate used in making the batch for potency, moisture, pH, residue on ignition, and identity.

(*c*) The batch for neomycin content, polymyxin content, and moisture.

(ii) Samples required:

(*a*) The neomycin sulfate used in making the batch: 10 packages, each containing approximately 300 milligrams.

(*b*) The polymyxin B sulfate used in making the batch: 10 packages, each containing approximately 300 milligrams.

(*c*) The batch: A minimum of 30 suppositories.

(*d*) In case of an initial request for certification, each other ingredient used in making the batch: One package of each containing approximately 5 grams.

(4) *Fees.* $4.00 for each package in the samples submitted in accordance with subparagraph (3)(ii) (*a*), (*b*), and (*d*) of this paragraph; $1.00 for each suppository submitted in accordance with subparagraph (3)(ii)(*c*) of this paragraph.

(b) *Tests and methods of assay*—(1) *Potency*—(i) *Neomycin content.* Proceed as directed in § 148i.1(b)(1), except prepare the sample for assay as follows: Place a representative number of suppositories into a high-speed glass blender with 1.0 milliliter of polysorbate 80 and sufficient 0.1*M* potassium phosphate buffer, pH 8.0, to give a stock solution of convenient concentration. Blend 3 to 5 minutes. Further dilute with 0.1*M* potassium phosphate buffer, pH 8.0, to the proper prescribed reference concentration. The content of neomycin is satisfactory if it contains not less than 90 percent and not more than 130 percent of the number of milligrams of neomycin that it is represented to contain.

(ii) *Polymyxin content.* Proceed as directed in § 148p.1(b)(1) of this chapter, except add to each concentration of the polymyxin standard curve a quantity of neomycin to yield the same concentration of neomycin as that present when the sample is diluted to contain 10 units of polymyxin per milliliter, and prepare the sample for assay as follows: Blend a representative number of suppositories in a high-speed glass blender, with 1.0 milliliter of polysorbate 80 and sufficient 10 percent potassium phosphate buffer, pH 6.0, to give a stock solution of convenient concentration. Further dilute with 10 percent potassium phosphate buffer, pH 6.0, to the reference concentration of 10 units of polymyxin per milliliter. Its content of polymyxin is satisfactory if it contains not less than 90 percent and not more than 130 percent of the number of units of polymyxin that it is represented to contain.

(2) *Moisture.* Proceed as directed in § 141a.8(b) of this chapter.

§ 148i.20 Neomycin sulfate-polymyxin B sulfate-gramicidin ophthalmic solution.

(a) *Requirements for certification*—(1) *Standards of identity, strength, quality, and purity.* Neomycin sulfate-polymyxin B sulfate-gramicidin ophthalmic solution is a solution containing, in each milliliter, 1.75 milligrams of neomycin, 5,000 units of polymyxin B, and 0.025 milligram of gramicidin, and with one or more suitable and harmless buffers, dispersants, and preservatives in a suitable and harmless isotonic aqueous vehicle. It is sterile. Its pH is not less than 4.7 and not more than 6.0. The neomycin sulfate used conforms to the standards prescribed by § 148i.1(a)(1)(i), (iv), (vi), and (vii). The polymyxin B sulfate used conforms to the standards prescribed by § 148p.1(a)(1)(i), (iv), (vi), (vii), and (ix) of this chapter. The gramicidin used conforms to the standards prescribed by § 148f.1(a)(1)(i), (ii), (iv), (v), and (vi) of this chapter. Each other substance used, if its name is recognized in the U.S.P. or N.F., conforms to the standards prescribed therefor by such official compendium.

(2) *Labeling.* It shall be labeled in accordance with the requirements of § 148.3 of this chapter. Its expiration date is 12 months.

(3) *Request for certification; samples.* In addition to the requirements of § 148.4 of this chapter, each such request shall contain:

(i) Results of tests and assays on:

(*a*) The neomycin sulfate used in making the batch for potency, toxicity, pH, and identity.

(*b*) The polymyxin B sulfate used in making the batch for potency, toxicity, pH, residue on ignition, and identity.

(*c*) The gramicidin used in making the batch for potency, toxicity, residue on ignition, melting point, crystallinity, and identity.

(*d*) The batch for neomycin content, polymyxin content, gramicidin content, sterility, and pH.

(ii) Samples required:

(*a*) The neomycin sulfate used in making the batch: 10 packages, each containing approximately 300 milligrams.

(*b*) The polymyxin B sulfate used in making the batch: 10 packages, each containing approximately 300 milligrams.

(*c*) The gramicidin used in making the batch: 10 packages, each containing approximately 500 milligrams.

(*d*) The batch:

(*1*) For all tests except sterility: A minimum of 7 immediate containers.

(*2*) For sterility testing: 10 immediate containers.

(*e*) In case of an initial request for certification, each other ingredient used in making the batch: One package of each containing approximately 5 grams.

(4) *Fees.* $4.00 for each package in the samples submitted in accordance with subparagraph (3)(ii) (*a*), (*b*), (*c*), and (*e*) of this paragraph; $6.00 for each immediate container submitted in accordance with subparagraph (3)(ii)(*d*)(*1*) of this paragraph; $10.00 for all im-

mediate containers in the sample submitted in accordance with subparagraph (3) (ii) (*d*) (*2*) of this paragraph.

(b) *Tests and methods of assay*—(1) *Potency*—(i) *Neomycin content.* Proceed as directed in § 148i.1(b) (1), except prepare the sample as follows: Remove an accurately measured portion and dilute with 0.1*M* potassium phosphate buffer, pH 8.0, to the proper prescribed reference concentration. The neomycin content is satisfactory if it is not less than 90 percent and not more than 130 percent of the number of milligrams of neomycin that it is represented to contain.

(ii) *Polymyxin content.* Remove an accurately measured portion and dilute with 10 percent potassium phosphate buffer, pH 6.0, to a reference concentration of 10 units of polymyxin per milliliter. Proceed as directed in § 148p.1(b) (1) of this chapter, except add to each concentration of the polymyxin standard curve a quantity of neomycin to yield the same concentration of neomycin as that present when the sample is diluted to contain 10 units of polymyxin per milliliter. If thimerosal is an ingredient adjust the seed layer medium to contain 300 milligrams of thioglycollic acid per liter. The polymyxin content is satisfactory if it is not less than 90 percent and not more than 130 percent of the number of units of polymyxin that it is represented to contain.

(iii) *Gramicidin content.* Proceed as directed in § 148f.1(b) (1) of this chapter, except to prepare the sample for assay remove a representative sample with a suitable syringe, place into an appropriate volumetric flask, and dilute with 95 percent alcohol to give a stock solution of convenient concentration. Make proper estimated dilutions in 95 percent alcohol to the reference concentration. The gramicidin content is satisfactory if it contains not less than 90 percent and not more than 130 percent of the number of milligrams of gramicidin that it is represented to contain.

(2) *Sterility.* Use 0.25 milliliter from each immediate container and proceed as directed in § 141a.2 of this chapter, except that neither penicillinase nor the control tube is used in the test for bacteria.

(3) *pH.* Proceed as directed in § 141a.5 (b) of this chapter, using the undiluted sample.

§ 148i.21 Neomycin sulfate-polymyxin B sulfate-gramicidin-hydrocortisone-hydroxyamphetamine hydrobromide-phenylephrine hydrochloride nasal solution.

(a) *Requirements for certification*—(1) *Standards of identity, strength, quality, and purity.* Neomycin sulfate-polymyxin B sulfate-gramicidin-hydrocortisone-hydroxyamphetamine hydrobromide-phenylephrine hydrochloride nasal solution is a solution containing, in each milliliter, 0.6 milligram of neomycin, 2,000 units of polymyxin B, 0.05 milligram of gramicidin, 0.2 milligram of hydrocortisone, 5.0 milligrams of hydroxyamphetamine hydrobromide, and 1.25 milligrams of phenylephrine hydrochloride. It contains one or more suitable and harmless buffers, dispersants, and preservatives in an aqueous vehicle. The pH is not less than 5.0 and not more than 6.0. The neomycin sulfate used conforms to the standards prescribed by § 148i.1(a) (1) (i), (iv), (vi), and (vii). The polymyxin B sulfate used conforms to the standards prescribed by § 148p.1 (a) (1) (i), (iv), (vi), (vii), and (ix) of this chapter. The gramicidin used conforms to the standards prescribed by § 148f.1(a) (1) (i), (ii), (iv), (v), and (vi) of this chapter. Each other substance used, if its name is recognized in the U.S.P. or N.F., conforms to the standards prescribed by such official compendium.

(2) *Labeling.* It shall be labeled in accordance with the requirements of § 148.3 of this chapter. Its expiration date is 12 months.

(3) *Request for certification; samples.* In addition to the requirements of § 148.4 of this chapter, each such request shall contain:

(i) Results of tests and assays on:

(*a*) The neomycin sulfate used in making the batch for potency, toxicity, pH, and identity.

(*b*) The polymyxin B sulfate used in making the batch for potency, toxicity, pH, residue on ignition, and identity.

(*c*) The gramicidin used in making the batch for potency, toxicity, crystallinity, residue on ignition, melting point, and identity.

(*d*) The batch for neomycin content, gramicidin content, and pH.

(ii) Samples required:

(*a*) The neomycin sulfate used in making the batch: 10 packages, each containing approximately 300 milligrams.

(*b*) The polymyxin B sulfate used in making the batch: 10 packages, each containing approximately 300 milligrams.

(*c*) The gramicidin used in making the batch: 10 packages, each containing approximately 500 milligrams.

(*d*) The batch: A minimum of 7 immediate containers.

(*e*) In case of an initial request for certification, each other ingredient used in making the batch: One package of each containing aproximately 5 grams.

(4) *Fees.* $4.00 for each package in the samples submitted in accordance with subparagraph (3) (ii) (*a*), (*b*), (*c*), and (*e*) of this paragraph; $6.00 for each immediate container submitted in accordance with subparagraph (3) (ii) (*d*) of this paragraph.

(b) *Tests and methods of assay*—(1) *Potency*—(i) *Neomycin content.* Proceed as directed in § 148i.20(b) (1) (i). Its content of neomycin is satisfactory if it is not less than 90 percent and not more than 125 percent of the number of milligrams of neomycin that it is represented to contain.

(ii) *Polymyxin content.* Proceed as directed in § 148i.20(b) (1) (ii). Its content of polymyxin is satisfactory if it is not less than 90 percent and not more than 140 percent of the number of units of polymyxin that it is represented to contain.

(iii) *Gramicidin content.* Proceed as directed in § 148i.20(b) (1) (iii). Its content of gramicidin is satisfactory if it is not less than 90 percent and not more than 125 percent of the number of milligrams of gramicidin that it is represented to contain.

(2) *pH.* Proceed as directed in § 141a.5(b) of this chapter, using the undiluted sample.

§ 148i.23 Neomycin sulfate-gramicidin-_____ ophthalmic solution; neomycin sulfate-gramicidin-_____ ophthalmic suspension (the blanks being filled in with the established name(s) of the other active ingredient(s) present in accordance with paragraph (a) (1) of this section).

(a) *Requirements for certification*—(1) *Standards of identity, strength, quality, and purity.* The drug is a solution or suspension in a suitable and harmless aqueous vehicle containing, in each milliliter, the following:

(i) 0.66 milligram of neomycin, 0.05 milligram of gramicidin, 1.25 milligrams of phenylephrine hydrochloride, and 1.25 milligrams of thonzylamine hydrochloride; or

(ii) 2.5 milligrams of neomycin, 0.025 milligram of gramicidin, and 1 milligram of fludrocortisone acetate; or

(iii) 2.5 milligrams of neomycin, 0.025 milligram of gramicidin, and 1.14 milligrams of fludrocortisone hemisuccinate.

It may also contain suitable and harmless buffers, dispersants, irrigants, and preservatives. It is sterile. Its pH is not less than 5.0 nor more than 7.5. The neomycin sulfate used conforms to the standards prescribed by § 148i.1(a) (1) (i), (iv), (vi), and (vii). The gramicidin used conforms to the standards prescribed by § 148f.1(a) (1) (i), (ii), (iv), and (vi) of this chapter. Each other substance used, if its name is recognized in the U.S.P. or N.F., conforms to the standards prescribed therefor by such official compendium.

(2) *Labeling.* It shall be labeled in accordance with the requirements of § 148.3 of this chapter. Its expiration date is 12 months.

(3) *Requests for certification; samples.* In addition to the requirements of § 148.4 of this chapter, each such request shall contain:

(i) Results of tests and assays on:

(*a*) The neomycin sulfate used in making the batch for potency, toxicity, pH, and identity.

(*b*) The gramicidin used in making the batch for potency, toxicity, crystallinity, residue on ignition, melting point, and identity.

(*c*) The batch for neomycin content, gramicidin content, sterility, and pH.

(ii) Samples required:

(*a*) The neomycin sulfate used in making the batch: 10 packages, each containing approximately 300 milligrams.

(*b*) The gramicidin used in making the batch: 10 packages, each containing approximately 500 milligrams.

(*c*) The batch:

(*1*) For all tests except sterility: A minimum of 6 immediate containers.

(*2*) For sterility testing: 10 immediate containers.

(*d*) In case of an initial request for certification, each other ingredient used in making the batch: One package of each containing approximately 5 grams.

(4) *Fees.* $4.00 for each package in the samples submitted in accordance with subparagraph (3) (ii) (*a*), (*b*), and (*d*) of this paragraph; $5.00 for each immediate container submitted in accordance with subparagraph (3) (ii) (*c*) (*1*) of this paragraph; $10.00 for all immediate containers in the sample submitted in accordance with subparagraph (3) (ii) (c) (2) of this paragraph.

(b) *Tests and methods of assay*—(1) *Potency*—(i) *Neomycin content.* Proceed as directed in § 148i.20(b) (1) (i). The neomycin content is satisfactory if it is not less than 90 percent and not more than 130 percent of the number of milligrams of neomycin that it is represented to contain.

(ii) *Gramicidin content.* Proceed as directed in § 148i.20(b) (1) (iii). The content of gramicidin is satisfactory if it is not less than 90 percent and not more than 130 percent of the number of milligrams of gramicidin that it is represented to contain.

(2) *Sterility.* Using 0.25 milliliter from each container, proceed as directed in § 141a.2 of this chapter, except that neither penicillinase nor the control tube is used in the test for bacteria.

(3) *pH.* Proceed as directed in § 141a.5(b) of this chapter, using the undiluted sample.

§ 148i.24 Neomycin sulfate-gramicidin-hydrocortisone-thonzylamine hydrochloride-thonzonium bromide otic solution.

(a) *Requirements for certification*—(1) *Standards of identity, strength, quality and purity.* Neomycin sulfate-gramicidin - hydrocortisone - thonzylamine hydrochloride-thonzonium bromide otic solution is a solution containing, in each milliliter, 0.66 milligram of neomycin, 0.05 milligram of gramicidin, 0.2 milligram of hydrocortisone, 10 milligrams of thonzylamine hydrochloride, and 0.5 milligram of thonzonium bromide, with one or more suitable and harmless buffers, dispersants, and preservatives, in a suitable and harmless isotonic aqueous vehicle. It is sterile. The pH is not less than 5.0 and not more than 6.0. The neomycin sulfate used conforms to the standards prescribed by § 148i.1(a) (1) (i), (vi), and (vii). The gramicidin used conforms to the standards prescribed by § 148f.1(a) (1) (i), (iv), (v), and (vi) of this chapter. Each other substance, used, if its name is recognized in the U.S.P. or N.F., conforms to the standards prescribed therefor by such official compendium.

(2) *Labeling.* It shall be labeled in accordance with the requirements of § 148.3 of this chapter. Its expiration date is 12 months.

(3) *Requests for certification; samples.* In addition to the requirements of § 148.4 of this chapter, each such request shall contain:

(i) Results of tests and assays on:

(*a*) The neomycin sulfate used in making the batch for potency, pH, and identity.

(*b*) The gramicidin used in making the batch for potency, crystallinity, residue on ignition, melting point, and identity.

(*c*) The batch for neomycin content, gramicidin content, sterility, and pH.

(ii) Samples required:

(*a*) The neomycin sulfate used in making the batch: 10 packages, each containing approximately 300 milligrams.

(*b*) The gramicidin used in making the batch: 10 packages, each containing approximately 500 milligrams.

(*c*) The batch:

(*1*) For all tests except sterility: A minimum of six immediate containers.

(2) For sterility: 10 immediate containers.

(*d*) In case of an initial request for certification, each other ingredient used in making the batch: One package of each containing approximately 5 grams.

(4) *Fees.* $4.00 for each package in the samples submitted in accordance with subparagraph (3) (ii) (*a*), (*b*), and (*d*) of this paragraph; $5.00 for each immediate container submitted in accordance with subparagraph (3) (ii) (*c*) (*1*) of this paragraph; $10.00 for all immediate containers in the sample submitted in accordance with subparagraph (3) (ii) (c) (2) of this paragraph.

(b) *Tests and methods of assay*—(1) *Potency*—(i) *Neomycin content.* Proceed as directed in § 148i.20(b) (1) (i). The neomycin content is satisfactory if it is not less than 90 percent and not more than 140 percent of the number of milligrams of neomycin that it is represented to contain.

(ii) *Gramicidin content.* Proceed as directed in § 148i.20(b) (1) (iii). The gramicidin content is satisfactory if it is not less than 90 percent and not more than 140 percent of the number of milligrams of gramicidin that it is represented to contain.

(2) *Sterility.* Use 0.25 milliliter from each immediate container and proceed as directed in § 141a.2 of this chapter, except that neither penicillinase nor the control tube is used in the test for bacteria.

(3) *pH.* Proceed as directed in § 141a.5(b) of this chapter, using the undiluted sample.

§ 148i.25 Neomycin sulfate-gramicidin-triamcinolone acetonide lotion; neomycin sulfate-gramicidin-fludrocortisone acetate lotion.

(a) *Requirements for certification*—(1) *Standards of identity, strength, quality and purity.* The drug is a lotion containing, in each milliliter, 2.5 milligrams of neomycin, 0.25 milligram of gramicidin, and either 1 milligram of triamcinolone acetonide or 1 milligram of fludrocortisone acetate, with one or more suitable and harmless emollients, buffers, dispersants, and preservatives, in a suitable and harmless lotion base. The neomycin sulfate used conforms to the standards prescribed by § 148i.1(a) (1) (i), (vi), and (vii). The gramicidin used conforms to the standards prescribed by § 148f.1(a) (1) (i), (iv), (v), and (vi) of this chapter. Each other substance used, if its name is recognized in the U.S.P. or N.F., conforms to the requirements prescribed therefor by such official compendium.

(2) *Labeling.* It shall be labeled in accordance with the requirements of § 148.3 of this chapter. Its expiration date is 12 months.

(3) *Requests for certification; samples.* In addition to the requirements of § 148.4 of this chapter, each such request shall contain:

(i) Results of tests and assays on:

(*a*) The neomycin sulfate used in making the batch for potency, pH, and identity.

(*b*) The gramicidin used in making the batch for potency, crystallinity, residue on ignition, melting point, and identity.

(*c*) The batch for neomycin content and gramicidin content.

(ii) Samples required:

(*a*) The neomycin sulfate used in making the batch: 10 packages, each containing approximately 300 milligrams.

(*b*) The gramicidin used in making the batch: 10 packages, each containing approximately 500 milligrams.

(*c*) The batch: A minimum of 6 immediate containers.

(*d*) In case of an initial request for certification, each other substance used in making the batch: One package of each containing approximately 5 grams.

(4) *Fees.* $4.00 for each package in the samples submitted in accordance with subparagraph (3) (ii) (*a*), (*b*), and (*d*) of this paragraph; $5.00 for each immediate container submitted in accordance with subparagraph (3) (ii) (*c*) of this paragraph.

(b) *Tests and methods of assay*—(1) *Potency*—(i) *Neomycin content.* Proceed as directed in § 148i.10(b) (1). Its neomycin content is satisfactory if it is not less than 90 percent and not more than 140 percent of the number of milligrams of neomycin that it is represented to contain.

(ii) *Gramicidin content.* Proceed as directed in § 148f.1(b) (1) of this chapter, except prepare the sample by placing an accurately measured representative portion into a high-speed glass blender with sufficient 95 percent alcohol to give a stock solution of convenient concentration. Blend 3 to 5 minutes. Make proper estimated dilutions in 95 percent alcohol to the reference concentration. Its gramicidin content is satisfactory if it is not less than 90 percent and not more than 140 percent of the number of milligrams of gramicidin that it is represented to contain.

§ 148i.26 Neomycin sulfate-gramicidin ointment; neomycin sulfate-gramicidin-triamcinolone acetonite ointment; neomycin sulfate-gramicidin-fludrocortisone acetate ointment.

(a) *Requirements for certification*—(1) *Standards of identity, strength, quality, and purity.* Neomycin sulfate-gramicidin ointment is an ointment containing, in each gram, 2.5 milligrams of neomycin and 0.25 milligram of gramicidin. Neomycin sulfate-gramicidin-triamcinolone acetonide ointment is an ointment containing, in each gram, 2.5 milligrams of neomycin, 0.25 milligrams of gramicidin, and 1.0 milligram of triamcinolone acetonide. Neomycin sulfate-gramicidin-fludrocortisone acetate ointment is an ointment containing, in each gram, 2.5 milligrams of neomycin, 0.25 milligram of gramicidin, and 1.0 milligram of fludrocortisone acetate. Their moisture content is not more than

1.0 percent. The neomycin sulfate used conforms to the standards prescribed by § 148i.1(a)(1) (i), (v), (vi), and (vii), and in addition if it is used in the preparation of an ophthalmic ointment, paragraph (a)(1)(iv) of that section. The gramicidin used conforms to the standards prescribed by § 148f.1(a)(1) (i), (iii), (iv), (v), and (vi) of this chapter, and in addition if it is used in the preparation of an ophthalmic ointment, paragraph (a)(1)(ii) of that section. Each other substance used, if its name is recognized in the U.S.P. or N.F., conforms to the standards prescribed therefor by such official compendium.

(2) *Labeling.* If it contains a steroid or it is intended for ophthalmic use, it shall be labeled in accordance with the requirements of § 148.3 of this chapter, and its expiration date is 12 months. If it does not contain a steroid or it is not intended for ophthalmic use, each package shall bear on its label or labeling, as hereinafter indicated, the following:

(i) On the label of the immediate container and on the outside wrapper or container, if any:

(*a*) The batch mark.

(*b*) The name and quantity of each active ingredient contained in the drug.

(*c*) An expiration date that is 12 months after the month during which the batch was certified.

(ii) On the label of the immediate container or other labeling attached to or within the package, adequate directions under which the layman can use the drug safely and efficaciously.

(3) *Requests for certification; samples.* In addition to the requirements of § 148.4 of this chapter, each such request shall contain:

(i) Results of tests and assays on:

(*a*) The neomycin sulfate used in making the batch for potency, moisture, pH, and identity, and in addition, if it is used in the preparation of an ophthalmic ointment, for toxicity.

(*b*) The gramicidin used in making the batch for potency, moisture, residue on ignition, melting point, crystallinity, and identity, and in addition, if it is used in the preparation of an ophthalmic ointment, for toxicity.

(*c*) The batch for neomycin content, gramicidin content, and moisture.

(ii) Samples required:

(*a*) The neomycin sulfate used in making the batch: 10 packages, each containing approximately 300 milligrams.

(*b*) The gramicidin used in making the batch: 10 packages, each containing approximately 500 miligrams.

(*c*) The batch: A minimum of six immediate containers.

(*d*) In case of an initial request for certification, each other ingredient used in making the batch: One package of each containing approximately 5 grams.

(4) *Fees.* $4.00 for each package in the samples submitted in accordance with subparagraph (3)(ii) (*a*), (*b*), and (*d*) of this paragraph; $5.00 for each immediate container submitted in accordance with subparagraph (3)(ii)(*c*) of this paragraph.

(b) *Tests and methods of assay*—(1) *Potency*—(i) *Neomycin content.* Proceed as directed in § 148i.3(b)(1). Its content of neomycin is satisfactory if it is not less than 90 percent and not more than 140 percent of the number of milligrams of neomycin that it is represented to contain.

(ii) *Gramicidin content.* Proceed as directed in § 148f.1(b)(1) of this chapter, except prepare the sample for assay by the following method: Place an accurately weighed representative portion into a separatory funnel. Dissolve the ointment in 50 milliliters of *n*-hexane. Extract this solution with four 50-milliliter portions of 80 percent alcohol. Collect the extractives in a 250-milliliter volumetric flask, bring to volume with 80 percent alcohol, and mix well. From this stock solution, dilute an aliquot with 95 percent alcohol to reference concentration.

Its content of gramicidin is satisfactory if it is not less than 90 percent and not more than 140 percent of the number of milligrams of gramicidin that it is represented to contain.

(2) *Moisture.* Proceed as directed in § 141a.8(b) of this chapter.

§ 148i.27 Neomycin sulfate-gramicidin-triamcinolone acetonide cream.

(a) *Requirements for certification*—(1) *Standards of identity, strength, quality, and purity.* Neomycin sulfate-gramicidin-triamcinolone acetonide cream is a cream containing 2.5 milligrams of neomycin, 0.25 milligram of gramicidin, and 1.0 milligram of triamcinolone acetonide per gram, with one or more suitable and harmless emollients, dispersants, and preservatives in a suitable and harmless cream base. The neomycin sulfate used conforms to the standards prescribed by § 148i.1(a)(1) (i), (vi), and (vii). The gramicidin used conforms to the standards prescribed by § 148f.1(a)(1) (i), (iv), (v), and (vi) of this chapter. Each other substance used, if its name is recognized in the U.S.P. or N.F., shall conform to the standards prescribed therefor by such official compendium.

(2) *Labeling.* It shall be labeled in accordance with the requirements prescribed by § 148.3 of this chapter. Its expiration date is 12 months.

(3) *Requests for certification; samples.* In addition to the requirements of § 148.4 of this chapter, each such request shall contain:

(i) Results of tests and assays on:

(*a*) The neomycin sulfate used in making the batch for potency, pH, and identity.

(*b*) The gramicidin used in making the batch for potency, residue on ignition, melting point, crystallinity and identity.

(*c*) The batch for neomycin content and gramicidin content.

(ii) Samples required:

(*a*) The neomycin sulfate used in making the batch: 10 packages, each containing approximately 300 milligrams.

(*b*) The gramicidin used in making the batch: 10 packages, each containing approximately 500 milligrams.

(*c*) The batch: A minimum of six immediate containers.

(*d*) In case of an initial request for certification, each other ingredient used in making the batch: One package of each containing approximately 5 grams.

(4) *Fees.* $5.00 for each immediate container in the samples submitted in accordance with subparagraph (3)(ii)(*c*) of this paragraph; $4.00 for each package in the samples submitted in accordance with subparagraph (3)(ii) (*a*), (*b*), and (*d*) of this paragraph.

(b) *Tests and methods of assay; potency*—(1) *Neomycin content.* Proceed as directed in § 148i.4(b)(1). Its neomycin content is satisfactory if it is not less than 90 percent and not more than 140 percent of the number of milligrams of neomycin that it is represented to contain.

(2) *Gramicidin content.* Proceed as directed in § 148f.1(b)(1) of this chapter, except to prepare the sample for assay proceed as follows: Place an accurately weighed representative portion into a high-speed glass blender and add sufficient 95 percent alcohol to give a stock solution of convenient concentration. Blend 3 to 5 minutes. Make proper estimated dilutions of an aliquot to the reference concentration with 95 percent alcohol. Its content of gramicidin is satisfactory if it is not less than 90 percent and not more than 140 percent of the number of milligrams of gramicidin that it is represented to contain.

§ 148i.28 [Reserved]

§ 148i.29 Neomycin sulfate-nystatin tablets.

(a) *Requirements for certification*—(1) *Standards of identity, strength, quality, and purity.* Neomycin sulfate-nystatin tablets are tablets containing 350 milligrams of neomycin and 125,000 units of nystatin per tablet, with suitable and harmless binders, lubricants, and colorings. The moisture content is not more than 10 percent. They shall disintegrate within 1 hour. The neomycin sulfate used conforms to the standards prescribed by § 148i.1(a)(1) (i), (iv), (v), (vi), and (vii). The nystatin used conforms to the standards prescribed by § 148k.1(a)(1) of this chapter. Each other substance used, if its name is recognized in the U.S.P. or N.F., conforms to the standards prescribed therefor by such official compendium.

(2) *Labeling.* It shall be labeled in accordance with the requirements of § 148.3 of this chapter. Its expiration date is 12 months.

(3) *Requests for certification; samples.* In addition to the requirements of § 148.4 of this chapter, each such request shall contain:

(i) Results of tests and assays on:

(*a*) The neomycin sulfate used in making the batch for potency, toxicity, moisture, pH, and identity.

(*b*) The nystatin used in making the batch for potency, toxicity, moisture, pH, and identity.

(*c*) The batch for neomycin content, nystatin content, moisture, and disintegration time.

(ii) Samples required:

(a) The neomycin sulfate used in making the batch: 10 packages, each containing approximately 300 milligrams.

(b) The nystatin used in making the batch: 10 packages, each containing approximately 300 milligrams.

(c) The batch:

(1) For all tests except disintegration time: A minimum of 30 tablets.

(2) For disintegration time: Six tablets.

(d) In case of an initial request for certification, each other ingredient used in making the batch: One package of each consisting of approximately 5 grams.

(4) *Fees.* $1.00 for each tablet submitted in accordance with subparagraph (3)(ii)(c)(1) of this paragraph; $3.00 for all tablets submitted in accordance with subparagraph (3)(ii)(c)(2) of this paragraph; $4.00 for each package in the samples submitted in accordance with subparagraph (3)(ii) (a), (b), and (d) of this paragraph.

(b) *Tests and methods of assay*—(1) *Potency*—(i) *Neomycin content.* Proceed as directed in § 148i.5(b)(1). Its content of neomycin is satisfactory if it is not less than 90 percent and not more than 120 percent of the number of milligrams of neomycin that it is represented to contain.

(ii) *Nystatin content.* Proceed as directed in § 148k.7(b)(1) of this chapter. Its content of nystatin is satisfactory if it is not less than 90 percent and not more than 120 percent of the number of units of nystatin that it is represented to contain.

(2) *Moisture.* Proceed as directed in § 141a.5(a) of this chapter.

(3) *Disintegration time.* Proceed as directed in § 141a.9(c) of this chapter.

Effective date. This order shall become effective 60 days from the date of its publication in the FEDERAL REGISTER.

(Sec. 507, 59 Stat. 463 as amended; 21 U.S.C. 357)

Dated: August 7, 1964.

GEO. P. LARRICK,
Commissioner of Food and Drugs.

[F.R. Doc. 64-8142; Filed, Aug. 13, 1964; 8:45 a.m.]

ANTIBIOTIC DRUGS; TESTS AND METHODS OF ASSAY AND CERTIFICATION

Miscellaneous Amendments

The Commissioner of Food and Drugs has evaluated the views and comments received in response to the notices of proposed rule-making published in the FEDERAL REGISTER of May 11 and May 15, 1963 (28 F.R. 4769, 4846), and has concluded that the following regulations should issue for the certification of certain antibiotic drugs subject to the Drug Amendments of 1962 (76 Stat. 785-787; Public Law 87-781). Therefore, pursuant to the provisions of the Federal Food, Drug, and Cosmetic Act (sec. 507, 59 Stat. 463 as amended; 21 U.S.C. 357), and under the authority delegated to him by the Secretary of Health, Education, and Welfare (21 CFR 2.90; 29 F.R. 471), Title 21 is amended by adding thereto the new sections set forth below:

PART 148b—AMPHOTERICIN

§ 148b.3 Amphotericin B lotion.

(a) *Requirements for certification*—(1) *Standards of identity, strength, quality, and purity.* Amphotericin B lotion is composed of amphotericin B in a suitable and harmless lotion vehicle. It contains suitable and harmless emollients, emulsifiers, coloring agents, diluents, preservatives, and perfumes. It contains 30 milligrams of amphotericin B per milliliter. Its pH is not less than 5.0 and not more than 7.0. The amphotericin B used conforms to the standards prescribed by § 148b.1(a)(1) (i), (ii), (v), (vi), and (vii). Each other substance used, if its name is recognized in the U.S.P. or N.F., conforms to the standards prescribed therefor by such official compendium.

(2) *Labeling.* It shall be labeled in accordance with the requirements of § 148.3 of this chapter. Its expiration date is 12 months.

(3) *Request for certification.* In addition to the requirements of § 148.4 of this chapter, each such request shall contain:

(i) Results of tests and assays on:

(a) The amphotericin B used in making the batch for potency, amphotericin A content, pH, residue on ignition, and identity.

(b) The batch for potency and pH.

(ii) Samples required:

(a) The amphotericin B used in making the batch: 10 packages, each containing not less than 500 milligrams.

(b) The batch: A minimum of 5 immediate containers.

(c) In case of an initial request for certification, each other ingredient used in making the batch: One package of each consisting of 5 grams.

(4) *Fees.* $4.00 for each package or immediate container submitted in accordance with subparagraph (3)(ii) of this paragraph.

(b) *Tests and methods of assay*—(1) *Potency.* Transfer a 2-milliliter aliquot, accurately measured, into a 250-milliliter volumetric flask. Dissolve in 98 milliliters of dimethyl sulfoxide and shake for 10 minutes on a mechanical shaker. Dilute an aliquot with dimethyl sulfoxide to a concentration of 20 micrograms of amphotericin B per milliliter. Further dilute an aliquot in 0.2*M* potassium phosphate buffer, pH 10.5, to a concentration of 1 microgram of amphotericin B per milliliter. Proceed as directed in § 148b.1(b)(1). The amphotericin B content is satisfactory if it contains not less than 90 percent and not more than 125 percent of the number of milligrams of amphotericin B per milliliter that it is represented to contain.

(2) *pH.* Proceed as directed in § 141a.5(b) of this chapter, using the undiluted solution.

PART 148c—COLISTIN

§ 148c.5 Sodium colistimethate for intramuscular use.

(a) *Requirements for certification*—(1) *Standards of identity, strength, quality, and purity.* Sodium colistimethate for intramuscular use is a dry mixture of this antibiotic and dibucaine hydrochloride, with or without a suitable and harmless buffer substance. It contains either 30 milligrams of colistimethate and 2 milligrams of dibucaine hydrochloride or 150 milligrams of colistimethate and 8 milligrams of dibucaine hydrochloride per vial. It is sterile. It is nonpyrogenic. It is nontoxic. When reconstituted as directed in the labeling, its pH is not less than 5.5 and not more than 6.5. Its moisture content is not more than 9 percent. The sodium colistimethate used conforms to the standards prescribed by § 148c.4(a)(1) (i), (v), (vi), (vii), (viii), and (ix). Each other substance used, if its name is recognized in the U.S.P. or the N.F., conforms to the standards prescribed therefor by such official compendium.

(2) *Labeling.* It shall be labeled in accordance with the requirements of § 148.3 of this chapter. Its expiration date is 12 months.

(3) *Request for certification.* In addition to the requirements of § 148.4 of this chapter, each such request shall contain:

(i) Results of tests and assays on:

(a) The sodium colistimethate used in making the batch for potency, histamine, pH, moisture, heavy metals, and identity.

(b) The batch for potency, sterility, toxicity, pyrogens, moisture, and pH.

(ii) Samples required:

(a) The sodium colistimethate used in making the batch: 10 containers, each containing approximately 500 milligrams.

(b) The batch:

(1) For all tests except sterility: A minimum of 10 immediate containers.

(2) For sterility testing: 10 immediate containers.

(c) In case of an initial request for certification, each other ingredient used in making the batch: One package of each containing approximately 5 grams.

(4) *Fees.* $5.00 for each container submitted in accordance with subparagraph (3)(ii)(b)(1) of this paragraph; $4.00 for each container submitted in accordance with subparagraph (3)(ii) (a) and (c) of this paragraph; $10.00 for all containers submitted in accordance with subparagraph (3)(ii)(b)(2) of this paragraph.

(b) *Tests and methods of assay*—(1) *Potency.* Proceed as directed in § 148c.4(b)(1), after suspending the drug as directed in the labeling and removing the entire contents of each vial with a syringe and needle. Its contents of colistimethate is satisfactory if it is not less than 90 percent and not more than 115 percent of the number of milligrams of colistimethate that it is represented to contain.

(2) *Sterility.* Proceed as directed in § 148c.4(b)(2), using the entire contents of each immediate container.

(3) *Pyrogens.* Proceed as directed in § 148c.4(b)(3).

(4) *Toxicity.* Proceed as directed in § 148c.4(b)(4).

(5) *Moisture.* Proceed as directed in § 141a.5(a) of this chapter.

(6) *pH.* Proceed as directed in § 141a.5(b) of this chapter, using the solution prepared as directed in the labeling.

PART 148i—NEOMYCIN SULFATE

§ 148i.32 Neomycin palmitate.

(a) *Requirements for certification*—(1) *Standards of identity, strength, quality, and purity.* Neomycin palmitate is the palmitate salt of a kind of neomycin or a mixture of two or more such salts. It is so purified and dried that:

(i) It has a potency of not less than 180 micrograms of neomycin per milligram.

(ii) Its moisture content is not more than 5 percent.

(iii) The pH of a solution containing 50 milligrams per milliliter in 80 percent methyl alcohol is not less than 6.5 and not more than 7.5.

(iv) It exhibits a positive identity test for neomycin and meets a specified melting range for palmitic acid which is derived from the palmitate salt.

(2) *Labeling.* It shall be labeled in accordance with the requirements of § 148.3(b) of this chapter. Its expiration date is 12 months.

(3) *Requests for certification.* In addition to the requirements of § 148.4 of this chapter, each such request shall contain:

(i) Results of tests and assays on the batch for potency, moisture, pH, and identity.

(ii) Samples required: 10 packages, each containing approximately 300 milligrams.

(4) *Fees.* $4.00 for each package in the samples submitted in accordance with subparagraph (3)(ii) of this paragraph.

(b) *Tests and methods of assay*—(1) *Potency.* Proceed as directed in § 148i.1(b)(1)(i), except prepare the sample in the following manner: Blend an accurately weighed sample of approximately 30 milligrams in 19.0 milliliters of methyl alcohol plus 1.0 milliliter of polysorbate 80. Use a high-speed glass blender. Transfer dropwise a 1.0 milliliter aliquot into that volume of 0.1*M* potassium phosphate buffer, pH 8.0, which will give a final (estimated) concentration of 1.0 microgram of neomycin per milliliter.

(2) *Moisture.* Proceed as directed in § 141a.5(a) of this chapter.

(3) *pH.* Proceed as directed in § 141.a-5(b) of this chapter, except prepare a solution containing 50 milligrams per milliliter in 80 percent methyl alcohol.

(4) *Identity*—(i) *Neomycin.* Add 1 gram of neomycin palmitate to 50 milliliters of methyl alcohol in a 100-milliliter beaker. Stir, and heat carefully to about 35° C. to dissolve. After the neomycin palmitate is in solution, carefully adjust the solution to pH 5.8±0.2 by the dropwise addition of sulfuric acid. Stir the solution while adding the acid. Allow to stand one-half hour. Filter off the precipitate and wash it with 5–8 milliliters of methyl alcohol. Save the entire methyl alcohol filtrate. Dry the precipitate thoroughly in an oven not exceeding 60° C. After drying, powder the material if necessary, transfer about 10 milligrams to a test tube (19 millimeters x 150 millimeters) and dissolve in 1 milliliter of water, and add 5 milliliters of 40 percent sulfuric acid solution. Heat in a boiling water bath 100 minutes. Allow to cool. Dilute to a volume of 25 milliliters with distilled water. Adjust a suitable recording ultraviolet spectrophotometer to zero absorbance from 220 mμ to 300 mμ, using an 8 percent sulfuric acid solution and 1-centimeter cells. Record the spectrum of the sample solution between these wavelengths. The ratio of the two absorbancies $\frac{(A278)}{(A232)}$ should not be less than 1.20 and not more than 1.50.

(ii) *Palmitate.* Evaporate to dryness the methyl alcohol filtrate obtained from the procedure described in subdivision (i) of this subparagraph. Dry the solid in vacuum for 2 hours at 40° C. Determine the melting point of the dried material. The melting point is not less than 57.0° C. nor more than 61.0° C. This indicates the purity of palmitic acid derived from neomycin palmitate.

§ 148i.33 Neomycin palmitate-hydrocortamate hydrochloride ointment with proteolytic enzymes.

(a) *Requirements for certification*—(1) *Standards of identity, strength, quality, and purity.* Neomycin palmitate-hydrocortamate hydrochloride ointment with proteolytic enzymes contains, in each gram, 3.5 milligrams of neomycin, 1.25 milligrams of hydrocortamate hydrochloride, and 10,000 suitable units of proteolytic enzyme activity, in a suitable and harmless ointment base. The moisture content is not more than 1.0 percent. The neomycin palmitate used conforms to the requirements of § 148i.32(a)(1). Each other substance used, if its name is recognized in the U.S.P. or N.F., conforms to the standards prescribed therefor by such official compendium.

(2) *Labeling.* It shall be labeled in accordance with the requirements of § 148.3 of this chapter. Its expiration date is 12 months.

(3) *Requests for certification.* In addition to the requirements of § 148.4 of this chapter, each such request shall contain:

(i) Results of tests and assays on:

(*a*) The neomycin palmitate used in making the batch for potency, moisture, pH, and identity.

(*b*) The batch for potency and moisture.

(ii) Samples required:

(*a*) The neomycin palmitate used in making the batch: 10 packages, each containing approximately 300 milligrams.

(*b*) The batch: A minimum of five immediate containers.

(*c*) In case of an initial request for certification, each other ingredient used in making the batch: One package of each containing approximately 5 grams.

(4) *Fees.* $4.00 for each package in the samples or each immediate container submitted in accordance with subparagraph (3)(ii) of this paragraph.

(b) *Tests and methods of assay*—(1) *Potency.* Proceed as directed in § 148i.32(b)(1), except prepare the sample for assay as follows: Place approximately 1 gram of the ointment, accurately weighed, in a high-speed glass blender with 1.0 milliliter of polysorbate 80 and 99.0 milliliters of absolute methyl alcohol. Blend 3 to 5 minutes. Make proper estimated dilutions in 0.1*M* potassium phosphate buffer, pH 8.0, to the reference concentration. The neomycin content is satisfactory if it is not less than 90 percent and not more than 115 percent of the number of milligrams of neomycin that it is represented to contain.

(2) *Moisture.* Proceed as directed in § 141a.8(b) of this chapter.

§ 148i.34 Neomycin sulfate-polymyxin B sulfate-gramicidin-benzocaine ointment.

(a) *Requirements for certification*—(1) *Standards of identity, strength, quality, and purity.* Neomycin sulfate-polymyxin B sulfate-gramicidin-benzocaine ointment is neomycin sulfate, polymyxin B sulfate, gramicidin, and benzocaine, with suitable and harmless preservatives, in white petrolatum. Each gram contains 3.5 milligrams of neomycin, 2,000 units of polymyxin B, 0.25 milligram of gramicidin, and 10 milligrams of benzocaine. The moisture content is not more than 1.0 percent. The neomycin sulfate used conforms to the standards prescribed by § 148i.1(a)(1) (i), (v), (vi), and (vii). The polymyxin B sulfate used conforms to the standards prescribed by § 148p.1(a)(1) (i), (v), (vi), (vii), and (ix) of this chapter. The gramicidin used conforms to the standards prescribed by § 148f.1(a)(1) (i), (iii), (iv), (v), and (vi) of this chapter. Each other ingredient used, if its name is recognized in the U.S.P. or N.F., conforms to the standards prescribed therefor by such official compendium.

(2) *Labeling.* Each package shall bear on its label or labeling, as hereinafter indicated, the following:

(i) On the label of the immediate container and on the outside wrapper or container, if any:

(*a*) The batch mark.

(*b*) The name and quantity of each active ingredient contained in the drug.

(*c*) An expiration date that is 12 months after the month during which the batch was certified.

(ii) On the label of the immediate container or other labeling attached to or within the package, adequate directions under which the layman can use the drug safely and efficaciously.

(3) *Requests for certification; samples.* In addition to the requirements of § 148.4 of this chapter, each such request shall contain:

(i) Results of tests and assays on:

(*a*) The neomycin sulfate used in making the batch for potency, moisture, pH, and identity.

(*b*) The polymyxin B sulfate used in making the batch for potency, moisture, pH, residue on ignition, and identity.

(*c*) The gramicidin used in making the batch for potency, moisture, residue on ignition, melting point, crystallinity, and identity.

(*d*) The batch for neomycin content, polymyxin B content, gramicidin content, and moisture.

(ii) Samples required:

(*a*) The neomycin sulfate used in making the batch: 10 packages, each containing approximately 300 milligrams.

(*b*) The polymyxin B sulfate used in making the batch: 10 packages, each containing approximately 300 milligrams.

(*c*) The gramicidin used in making the batch: 10 packages, each containing approximately 500 milligrams.

(*d*) The batch: A minimum of seven immediate containers.

(*e*) In case of an initial request for certification, each other ingredient used in making the batch: One package of each containing approximately 5 grams.

(4) *Fees.* $6.00 for each immediate container submitted in accordance with subparagraph (3) (ii) (*d*) of this paragraph; $4.00 for each package in the samples submitted in accordance with subparagraph (3) (ii) (*a*), (*b*), (*c*), and (*e*) of this paragraph.

(b) *Tests and methods of assay*—(1) *Potency*—(i) *Neomycin content.* Proceed as directed in § 148i.3(b) (1) (i) or (ii). The content of nemoycin is satisfactory if it is not less than 90 percent and not more than 120 percent of the number of milligrams of neomycin that it is represented to contain.

(ii) *Polymyxin B content.* Proceed as directed in § 148i.16(b) (1) (ii) of this chapter. The content of polymyxin B is satisfactory if it is not less than 90 percent and not more than 120 percent of the number of units of polymyxin B that it is represented to contain.

(iii) *Gramicidin content.* Proceed as directed in § 148f.1(b) (1) of this chapter, except prepare the sample for assay as follows: Place approximately 1 gram of the ointment, accurately weighed, into a high-speed glass blender. Add that quantity of 95 percent ethyl alcohol which is sufficient to give a stock solution of convenient concentration. Blend 3 to 5 minutes. Make proper estimated dilutions of an aliquot to the reference concentration with 95 percent alcohol. The content of gramicidin is satisfactory if it is not less than 90 percent and not more than 120 percent of the number of milligrams of gramicidin that it is represented to contain.

(2) *Moisture.* Proceed as directed in § 141a.8(b) of this chapter.

§ 148i.35 Neomycin sulfate solution with radiopaque agent.

(a) *Requirements for certification*—(1) *Standards of identity, strength, quality, and purity.* Neomycin sulfate solution with radiopaque agent is neomycin sulfate with either methiodal sodium or methylglucamine diatrizoate, as radiopaque agents, and with or without one or more suitable and harmless antioxidants, preservatives, buffers and sequestering agents, in a sterile aqueous vehicle. Each milliliter contains 25.0 milligrams of neomycin. The content of the radiopaque agent is, in each milliliter, either 300 milligrams of methylglucamine diatrizoate or 200 milligrams of methiodal sodium. It is sterile. It is nontoxic. Its pH is not less than 5.0 and not more than 8.0 if it contains methiodal sodium and not less than 6.0 and not more than 7.6 if it contains methylglucamine diatrizoate. The neomycin sulfate used conforms to the standards prescribed by § 148i.1(a) (1) (i), (v), (vi), and (vii). Each other ingredient used, if its name is recognized in the U.S.P. or N.F., conforms to the standards prescribed therefor by such official compendium.

(2) *Labeling.* It shall be labeled in accordance with the requirements of § 148.3 of this chapter. Its expiration date is 12 months.

(3) *Request for certification.* In addition to the requirements of § 148.4 of this chapter, each such request shall contain:

(i) Results of tests and assays on:

(*a*) The neomycin sulfate used in making the batch for potency, moisture, pH, and identity.

(*b*) The batch for potency, sterility, toxicity, and pH.

(ii) Samples required:

(*a*) The neomycin sulfate used in making the batch: 10 packages, each containing approximately 300 milligrams.

(*b*) The batch:

(*1*) For all tests except sterility: Five immediate containers.

(*2*) For sterility testing: 10 immediate containers.

(*c*) In case of an initial request for certification, each other ingredient used in making the batch: One package of each containing approximately 5 grams.

(4) *Fees.* $4.00 for each package or immediate container in the samples submitted in accordance with subparagraph (3) (ii) (*a*), (*b*) (*1*), and (*c*) of this paragraph; $10.00 for all immediate containers submitted in accordance with subparagraph (3) (ii) (*b*) (*2*) of this paragraph.

(b) *Tests and methods of assay*—(1) *Potency.* Proceed as directed in § 148i.1 (b) (1), except prepare the sample for assay as follows: Transfer 1.0 milliliter into a 500-milliliter volumetric flask. Dilute to volume with 0.1*M* potassium phosphate buffer, pH 8.0, and mix well. Dilute an aliquot to the desired reference concentration with 0.1*M* potassium phosphate buffer, pH 8.0. The content of neomycin is satisfactory if it is not less than 90 percent and not more than 125 percent of the number of milligrams of neomycin that it is represented to contain.

(2) *Sterility.* Proceed as directed in § 141.2 of this chapter, except transfer aseptically 15 milliliters from each immediate container and filter the entire amount through a 0.45 micron filter. Neither penicillinase nor the control tube is used in the test for bacteria.

(3) *Toxicity.* Proceed as directed in § 141a.4 of this chapter, except use a test dose of 0.1 milliliter of a solution containing 1.0 milligram of neomycin per milliliter in sterile, distilled water.

(4) *pH.* Proceed as directed in § 141a.5(b) of this chapter, using the undiluted solution.

* * * * *

§ 148i.39 Neomycin sulfate-hydrocortisone acetate eye-ear drops; neomycin sulfate-prednisolone acetate eye-ear drops.

(a) *Requirements for certification*—(1) *Standards of identity, strength, quality, and purity.* Neomycin sulfate-hydrocortisone acetate eye-ear drops is an aqueous suspension containing, in each milliliter, 3.5 milligrams of neomycin and 5 milligrams or 15 milligrams of hydrocortisone acetate. Neomycin sulfate-prednisolone acetate eye-ear drops is an aqueous suspension containing, in each milliliter, 3.5 milligrams of neomycin and 2.5 milligrams of prednisolone acetate. The vehicle contains one or more suitable and harmless buffers, preservatives, and dispersants. It is sterile. Its pH is not less than 5.5 and not more than 7.5. The neomycin sulfate used conforms to the standards prescribed by § 148i.1(a) (1) (i), (iv), (v), (vi), and (vii). Each other substance used, if its name is recognized in the U.S.P. or N.F., conforms to the standards prescribed therefor by such official compendium.

(2) *Labeling.* It shall be labeled in accordance with the requirements of § 148.3 of this chapter. Its expiration date is 12 months.

(3) *Requests for certification.* In addition to the requirements of § 148.4 of this chapter, each such request shall contain:

(i) Results of tests and assays on:

(*a*) The neomycin sulfate used in making the batch for potency, toxicity, moisture, pH, and identity.

(*b*) The batch for potency, sterility, and pH.

(ii) Samples required:

(*a*) The neomycin sulfate used in making the batch: 10 packages, each containing approximately 300 milligrams.

(*b*) The batch:

(*1*) For all tests except sterility: A minimum of 5 immediate containers.

(*2*) For sterility testing: 10 immediate containers.

(*c*) In case of an initial request for certification, each other ingredient used in making the batch: One package of each containing approximately 5 grams.

(4) *Fees.* $4.00 for each immediate container or package submitted in accordance with subparagraph (3) (ii) (*a*), (*b*) (*1*), and (*c*) of this paragraph; $10.00 for all immediate containers submitted in accordance with subparagraph (3) (ii) (*b*) (*2*) of this paragraph.

(b) *Tests and methods of assay*—(1) *Potency.* Proceed as directed in § 148i.1 (b) (1), except prepare the sample for assay as follows: Remove 1.0 milliliter with a suitable syringe, place into an appropriate-sized volumetric flask and dilute to volume with 0.1*M* potassium phosphate buffer, pH 8.0, to give a stock solution of convenient concentration. Make proper estimated dilutions to the prescribed reference concentration with 0.1*M* potassium phosphate buffer, pH 8.0. The content of neomycin is satisfactory if it is not less than 90 percent and not more than 130 percent of the number

of milligrams of neomycin that it is represented to contain.

(2) *Sterility.* Use 0.25 milliliter from each immediate container, and proceed as directed in § 141a.2 of this chapter, except that neither penicillinase nor the control tube is used in the test for bacteria.

(3) *pH.* Proceed as directed in § 141a.5 (b) of this chapter, using the undiluted sample.

* * * * *

PART 148j—NOVOBIOCIN

§ 148j.6 Sodium novobiocin for injection.

(a) *Requirements for certification*—(1) *Standards of identity, strength, quality, and purity.* Sodium novobiocin for injection is sodium novobiocin with or without one or more suitable solubilizing agents, preservatives, and diluents. Each vial contains 500 milligrams of novobiocin. It is sterile. It is nonpyrogenic. It is nontoxic. Its moisture content is not more than 6.0 percent. Its pH, when reconstituted as directed in the labeling, is not less than 6.5 and not more than 8.5. The sodium novobiocin used conforms to the standards prescribed by § 148j.1(a)(1) (i), (v), (vi), (vii), (viii), and (ix). Each other substance used, if its name is recognized in the U.S.P. or N.F., conforms to the standards prescribed therefor by such official compendium.

(2) *Labeling.* It shall be labeled in accordance with the requirements of § 148.3 of this chapter. Its expiration date is 12 months.

(3) *Request for certification.* In addition to the requirements of § 148.4 of this chapter, each such request shall contain:

(i) Results of tests and assays on:

(*a*) The sodium novobiocin used in making the batch for potency, moisture, pH, residue on ignition, specific rotation, crystallinity, and identity.

(*b*) The batch for potency, sterility, pyrogens, toxicity, moisture, and pH.

(ii) Samples required:

(*a*) The sodium novobiocin used in making the batch: 10 packages, each containing approximately 500 milligrams.

(*b*) The batch:

(*1*) For all tests except sterility: A minimum of 10 immediate containers.

(2) For sterility testing: 10 immediate containers.

(*c*) In case of an initial request for certification, each other ingredient used in making the batch: One package of each containing not less than 5 grams.

(4) *Fees.* $4.00 for each package in the samples submitted in accordance with subparagraph (3)(ii) (*a*) and (*c*) of this paragraph; $5.00 for each immediate container in the sample submitted in accordance with subparagraph (3)(ii)(*b*)(*1*) of this paragraph; $10.00 for all containers submitted in accordance with subparagraph (3)(ii)(*b*)(2) of this paragraph.

(b) *Tests and methods of assay*—(1) *Potency.* Reconstitute as directed in the labeling, withdraw a representative sample with a suitable syringe fitted with a 22-gage needle and transfer to an appropriate-sized volumetric flask. Proceed as directed in § 148j.1(b)(1). The content of novobiocin is satisfactory if it is not less than 90 percent and not more than 120 percent of the number of milligrams of novobiocin that it is represented to contain.

(2) *Sterility.* Proceed as directed in § 148j.1(b)(2).

(3) *Pyrogens.* Proceed as directed in § 148j.1(b)(3).

(4) *Toxicity.* Proceed as directed in § 148j.1(b)(4).

(5) *Moisture.* Proceed as directed in § 141a.5(a) of this chapter.

(6) *pH.* Proceed as directed in § 141a.5(b) of this chapter, using the sample after reconstituting as directed in the labeling.

§ 148j.7 Sodium novobiocin capsules.

(a) *Requirements for certification*—(1) *Standards of identity, strength, quality, and purity.* Sodium novobiocin capsules are gelation capsules containing crystalline sodium novobiocin with a suitable and harmless filler and with or without a binder and a lubricant. Each capsule contains 100 milligrams or 250 milligrams of novobiocin. The moisture content is not more than 6.0 percent. The crystalline sodium novobiocin used conforms to the standards prescribed by § 148j.1(a)(1) (i), (iv), (v), (vi), (vii), (viii), and (ix). Each other substance used, if its name is recognized in the U.S.P. or N.F., conforms to the standards prescribed therefor by such official compendium.

(2) *Labeling.* It shall be labeled in accordance with the requirements of § 148.3 of this chapter. Its expiration date is 12 months.

(3) *Requests for certification.* In addition to the requirements of § 148.4 of this chapter, each such request shall contain:

(i) Results of tests and assays on:

(*a*) The sodium novobiocin used in making the batch for potency, toxicity, moisture, pH, residue on ignition, specific rotation, crystallinity, and identity.

(*b*) The batch for potency and moisture.

(ii) Samples required:

(*a*) The sodium novobiocin used in making the capsules: 10 packages, each containing approximately 500 milligrams.

(*b*) The batch: A minimum of 30 capsules.

(*c*) In case of an initial request for certification, each other ingredient used in making the batch: One package of each containing approximately 5 grams.

(4) *Fees.* $0.75 for each capsule submitted in accordance with subparagraph (3)(ii)(*b*) of this paragraph; $4.00 for each package in the samples submitted in accordance with subparagraph (3)(ii) (*a*) and (*c*) of this paragraph.

(b) *Tests and methods of assay*—(1) *Potency.* Proceed as directed in § 148j.1 (b)(1) of this chapter, except prepare the sample for assay as follows: Place a representative number of capsules in a high-speed glass blender with 1.0 milliliter of polysorbate 80 and sufficient 0.1*M* potassium phosphate buffer, pH 8.0, to give a stock solution of convenient concentration. Blend 3 to 5 minutes. The content of novobiocin is satisfactory if it is not less than 90 percent and not more than 120 percent of the number of milligrams of novobiocin that it is represented to contain.

(2) *Moisture.* Proceed as directed in § 141a.5(a) of this chapter.

Effective date. This order shall become effective 60 days from the date of its publication in the FEDERAL REGISTER.

(Sec. 507, 59 Stat. 463 as amended; 21 U.S.C. 357)

Dated: August 7, 1964.

GEO. P. LARRICK,
Commissioner of Food and Drugs.

[F.R. Doc. 64-8141; Filed, Aug. 13, 1964; 8:45 a.m.]